

PRV SE 03 / 1956

PATENT- OCH REGISTRERINGSVERKET
Patentavdelningen

REC'D 14 JAN 2004

WIPO

PCT

PCT/SE 03 / 01 956

15 -12- 2003

PCT/SE 03 / 01 956

Intyg
Certificate

Härmed intygas att bifogade kopior överensstämmer med de handlingar som ursprungligen ingivits till Patent- och registreringsverket i nedannämnda ansökan.

Ansökan ingavs ursprungligen på engelska.

This is to certify that the annexed is a true copy of the documents as originally filed with the Patent- and Registration Office in connection with the following patent application.

The application was originally filed in English.

(71) Sökande AstraZeneca AB, Södertälje SE
Applicant (s)

(21) Patentansökningsnummer 0203752-1
Patent application number

(86) Ingivningsdatum 2002-12-17
Date of filing

Stockholm, 2003-10-23

För Patent- och registreringsverket
For the Patent- and Registration Office

Hjördis Segerlund
Hjördis Segerlund

Avgift
Fee 170:-

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH
RULE 17.1(a) OR (b)

PCT/AU02/10-17

NEW COMPOUNDS

5

FIELD OF THE INVENTION

The present invention relates to new compounds of formula I, as a free base or a pharmaceutically acceptable salt, solvate or solvate of salt thereof, to pharmaceutical formulations containing said compounds and to the use of said compounds in therapy. The present invention further relates to a process for the preparation of compounds of formula I and to new intermediates used therein.

15 **BACKGROUND OF THE INVENTION**

Glycogen synthase kinase 3 (GSK3) is a serine / threonine protein kinase composed of two isoforms (α and β), which are encoded by distinct genes but are highly homologous within the catalytic domain. GSK3 is highly expressed in the central and peripheral nervous system. GSK3 phosphorylates several substrates including tau, β -catenin, glycogen synthase, pyruvate dehydrogenase and elongation initiation factor 2b (eIF2b). Insulin and growth factors activate protein kinase B, which phosphorylates GSK3 on serine 9 residue and inactivates it.

25 *Alzheimer's Disease (AD) dementias, and taupathies.*

AD is characterized by cognitive decline, cholinergic dysfunction and neuronal death, neurofibrillary tangles and senile plaques consisting of amyloid- β deposits. The sequence of these events in AD is unclear, but is believed to be related. Glycogen synthase kinase 3 β (GSK3 β) or Tau (τ) phosphorylating kinase selectively phosphorylates the microtubule associated protein τ in neurons at sites that are hyperphosphorylated in AD brains. Hyperphosphorylated protein τ has lower affinity for microtubules and accumulates as paired helical filaments, which are the main components that constitute neurofibrillary

PRU/W/2-12-17

tangles and neuropil threads in AD brains. This results in depolymerization of microtubules, which leads to dying back of axons and neuritic dystrophy. Neurofibrillary tangles are consistently found in diseases such as AD, amyotrophic lateral sclerosis, parkinsonism-dementia of Gaun, corticobasal degeneration, dementia pugilistica and head trauma, Down's syndrome, postencephalitic parkinsonism, progressive supranuclear palsy, Niemann-Pick's Disease and Pick's Disease. Addition of amyloid- β to primary hippocampal cultures results in hyperphosphorylation of τ and a paired helical filaments-like state via induction of GSK3 β activity, followed by disruption of axonal transport and neuronal death (Imahori and Uchida., J. Biochem 121:179-188, 1997). GSK3 β 5 preferentially labels neurofibrillary tangles and has been shown to be active in pre-tangle neurons in AD brains. GSK3 protein levels are also increased by 50% in brain tissue from 10 AD patients. Furthermore, GSK3 β phosphorylates pyruvate dehydrogenase, a key enzyme in the glycolytic pathway and prevents the conversion of pyruvate to acetyl-Co-A (Hoshi et al., PNAS 93:2719-2723, 1996). Acetyl-Co-A is critical for the synthesis of acetylcholine, 15 a neurotransmitter with cognitive functions. Thus, GSK3 β inhibition may have beneficial effects in progression as well as the cognitive deficits associated with Alzheimer's disease and other above-referred to diseases.

Chronic and Acute Neurodegenerative Diseases.

Growth factor mediated activation of the PI3K /Akt pathway has been shown to play a key 20 role in neuronal survival. The activation of this pathway results in GSK3 β inhibition. Recent studies (Bhat et. al., PNAS 97:11074-11079 (2000)) indicate that GSK3 β activity is increased in cellular and animal models of neurodegeneration such as cerebral ischemia or after growth factor deprivation. For example, the active site phosphorylation was increased 25 in neurons vulnerable to apoptosis, a type of cell death commonly thought to occur in chronic and acute degenerative diseases such as Alzheimer's Disease, Parkinson's Disease, amyotrophic lateral sclerosis, Huntington's Disease and HIV dementia, ischemic stroke and head trauma. Lithium was neuroprotective in inhibiting apoptosis in cells and in the brain at doses that resulted in the inhibition of GSK3 β . Thus GSK3 β inhibitors could be 30 useful in attenuating the course of neurodegenerative diseases.

Bipolar Disorders (BD)

Bipolar Disorders are characterised by manic episodes and depressive episodes. Lithium has been used to treat BD based on its mood stabilising effects. The disadvantage of lithium is the narrow therapeutic window and the danger of overdosing that can lead to lithium intoxication. The recent discovery that lithium inhibits GSK3 at therapeutic concentrations has raised the possibility that this enzyme represents a key target of lithium's action in the brain (Stambolic et al., Curr. Biol. 6:1664-1668, 1996; Klein and Melton; PNAS 93:8455-8459, 1996). Inhibition of GSK3 β may therefore be of therapeutic relevance in the treatment of BD as well as in AD patients that have affective disorders.

Schizophrenia

GSK3 is involved in signal transduction cascades of multiple cellular processes, particularly during neural development. Kozlovsky et al (Am J Psychiatry 2000 May;157(5):831-3) found that GSK3 β levels were 41% lower in the schizophrenic patients than in comparison subjects. This study indicates that schizophrenia involves neurodevelopmental pathology and that abnormal GSK3 regulation could play a role in schizophrenia. Furthermore, reduced β -catenin levels have been reported in patients exhibiting schizophrenia (Cotter et al., Neuroreport 9:1379-1383 (1998)).

20

Diabetes

Insulin stimulates glycogen synthesis in skeletal muscles via the dephosphorylation and thus activation of glycogen synthase. Under resting conditions, GSK3 phosphorylates and inactivates glycogen synthase via dephosphorylation. GSK3 is also over-expressed in muscles from Type II diabetic patients (Nikoulina et al., Diabetes 2000 Feb;49(2):263-71). Inhibition of GSK3 increases the activity of glycogen synthase thereby decreasing glucose levels by its conversion to glycogen. GSK3 inhibition may therefore be of therapeutic relevance in the treatment of Type I and Type II diabetes and diabetic neuropathy.

30

Hair Loss

GSK3 phosphorylates and degrades β -catenin. β -catenin is an effector of the pathway for keratinin synthesis. β -catenin stabilisation may be lead to increase hair development. Mice

expressing a stabilised β -catenin by mutation of sites phosphorylated by GSK3 undergo a process resembling de novo hair morphogenesis (Gat et al., Cell 1998 Nov 25;95 (5):605-14)). The new follicles formed sebaceous glands and dermal papilla, normally established only in embryogenesis. Thus GSK3 inhibition may offer treatment for baldness.

5

Oral contraceptives

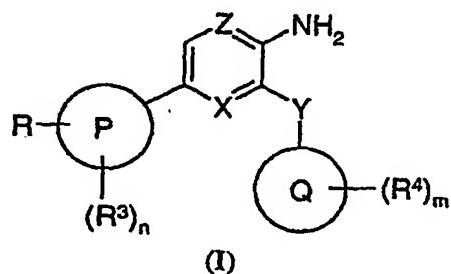
- Vijayaraghavan et al. (Biol Reprod 2000 Jun; 62 (6):1647-54) reported that GSK3 is high in motile versus immotile sperm. Immunocytochemistry revealed that GSK3 is present in the flagellum and the anterior portion of the sperm head. These data suggest that GSK3 could be a key element underlying motility initiation in the epididymis and regulation of mature sperm function. Inhibitors of GSK3 could be useful as contraceptives for males.

10

DISCLOSURE OF THE INVENTION

15

The object of the present invention is to provide compounds having a selective inhibiting effect at GSK3 as well as having a good bioavailability. The compounds fall within the generic formula I:



wherein:

Z is N;

Y is CONR⁵;

X is N;

P is phenyl;

20

25

Q is phenyl or a 5 or 6 membered heteroaromatic ring containing one or more heteroatoms selected from N, O or S;

R is selected from $C_{0-6}\text{alkyl}(SO_2)NR^1R^2$, $C_{0-6}\text{alkyl}CONR^1R^2$ and $OC_{1-6}\text{alkyl}NR^1R^2$;

R^1 and R^2 are independently selected from hydrogen, $C_{1-6}\text{alkyl}$, $C_{1-6}\text{alkyl}NR^6R^7$,

5 $C_{1-6}\text{alkyl}OR^6$ and a 5 or 6 membered heterocyclic ring containing one or more heteroatoms independently selected from N, O, or S and said heterocyclic ring may be optionally substituted by A;

10 R^1 and R^2 may together form a substituted 5 or 6 membered heterocyclic ring containing one or more heteroatoms independently selected from N, O, or S one or more heteroatoms independently selected from N, O or S and said heterocyclic ring may be optionally substituted by A;

15 R^3 and R^4 is independently selected from halo, nitro, trifluoromethyl, $C_{0-6}\text{alkyl}CN$, $C_{0-6}\text{alkyl}OR^6$, $C_{0-6}\text{alkyl}CONR^6R^7$, $C_{0-6}\text{alkyl}NR^6(CO)R^7$, $C_{0-6}\text{alkyl}COR^6$, $C_{0-6}\text{alkyl}(SO_2)NR^6R^7$;

20 m is 0 or 1;

n is 0;

R^5 is hydrogen;

25 R^6 and R^7 are independently selected from hydrogen and $C_{1-6}\text{alkyl}$;

R^6 and R^7 may together form a substituted 5 or 6 membered heterocyclic ring containing

30 one or more heteroatoms independently selected from N, O, or S one or more heteroatoms independently selected from N, O or S and said heterocyclic ring may be optionally substituted by A;

A is $C_{1-6}\text{alkyl}$;

25 as a free base or a pharmaceutically acceptable salt, solvate or solvate of a salt thereof.

In one aspect of the invention the following compounds are provided:

3-Amino-6-[4-({[(1R)-2-methoxy-1-methylethyl]amino}sulfonyl)phenyl]-N-pyridin-3-ylpyrazine-2-carboxamide hydrochloride;

30 3-Amino-6-[4-({[(1S)-2-methoxy-1-methylethyl]amino}sulfonyl)phenyl]-N-pyridin-3-ylpyrazine-2-carboxamide hydrochloride;

3-Amino-N-(3-nitrophenyl)-6-[4-(pyrrolidin-1-ylsulfonyl)phenyl]pyrazine-2-carboxamide;

PPUJ02-12-17

- 3-Amino-6-[4-(pyrrolidin-1-ylsulfonyl)phenyl]-N-1*H*-tetrazol-5-ylpyrazine-2-carboxamide;
- 5 3-Amino-*N*-(2-methoxyphenyl)-6-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}pyrazine-2-carboxamide hydrochloride;
- 10 3-Amino-6-{[(2-ethoxyethyl)amino]sulfonyl}phenyl)-*N*-pyridin-3-ylpyrazine-2-carboxamide hydrochloride;
- 15 3-Amino-*N*-(4-methoxyphenyl)-6-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}pyrazine-2-carboxamide hydrochloride;
- 20 3-Amino-*N*-[2-(aminocarbonyl)phenyl]-6-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}pyrazine-2-carboxamide hydrochloride;
- 25 3-Amino-*N*-[3-(aminocarbonyl)phenyl]-6-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}pyrazine-2-carboxamide hydrochloride;
- 30 3-Amino-*N*-(3-cyanophenyl)-6-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}pyrazine-2-carboxamide hydrochloride;
- 35 3-Amino-*N*-(2-bromophenyl)-6-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}pyrazine-2-carboxamide hydrochloride;
- 40 3-Amino-*N*-(3-bromophenyl)-6-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}pyrazine-2-carboxamide hydrochloride;
- 45 3-Amino-6-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}-*N*-1*H*-pyrazol-3-ylpyrazine-2-carboxamide hydrochloride;
- 3-Amino-*N*-[4-(aminocarbonyl)-1*H*-pyrazol-3-yl]-6-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}pyrazine-2-carboxamide hydrochloride;
- 3-Amino-*N*-1*H*-imidazol-2-yl-6-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}pyrazine-2-carboxamide hydrochloride;
- 3-amino-6-[3-fluoro-4-[2-(4-morpholinyl)ethoxy]phenyl]-*N*-3-pyridinyl-2-pyrazinecarboxamide hydrochloride;
- 3-Amino-6-{4-[(1-ethyl-3-piperidinyl)amino]sulfonyl}phenyl]-*N*-3-pyridinyl-2-pyrazinecarboxamide hydrochloride;
- 3-Amino-6-{4-[[bis(2-methoxyethyl)amino]sulfonyl]phenyl}-*N*-3-pyridinyl-2-pyrazinecarboxamide hydrochloride;

- 3-Amino-6-[4-[[3-methylbutyl]amino]sulfonyl]phenyl]-N-3-pyridinyl-2-pyrazinecarboxamide hydrochloride;
- 5 3-Amino-6-[4-[[[(1*S*)-2-methoxy-1-methylethyl]amino]carbonyl]phenyl]-N-3-pyridinyl-2-pyrazinecarboxamide hydrochloride;
- 10 3-Amino-N-3-pyridinyl-6-[4-[[[2-(1-pyrrolidinyl)ethyl]amino]carbonyl]phenyl]-2-pyrazinecarboxamide hydrochloride;
- 15 N-(3-Acetylphenyl)-3-amino-6-[4-[(4-methyl-1-piperazinyl)sulfonyl]phenyl]-2-pyrazinecarboxamide hydrochloride;
- 20 3-Amino-6-[4-[(4-methyl-1-piperazinyl)sulfonyl]phenyl]-N-[3-(trifluoromethyl)phenyl]-2-pyrazinecarboxamide hydrochloride;
- 25 N-[3-(Acetylamino)phenyl]-3-amino-6-[4-[(4-methyl-1-piperazinyl)sulfonyl]phenyl]-2-pyrazinecarboxamide;
- 30 3-Amino-N-[3-(aminosulfonyl)phenyl]-6-[4-[(4-methyl-1-piperazinyl)sulfonyl]phenyl]-2-pyrazinecarboxamide;
- 35 as a free base or an alternative a pharmaceutically acceptable salt, solvate or solvate of a salt thereof.

In yet another aspect of the invention the following compounds, which are useful as intermediates in the preparation of compounds of formula I, are provided:

- 30 3-Amino-6-bromo-N-pyridin-3-ylpyrazine-2-carboxamide;
- 35 1-[(4-Bromophenyl)sulfonyl]pyrrolidine;
- 40 4-(Pyrrolidin-1-ylsulfonyl)phenylboronic acid;
- 45 4-Bromo-N-[(1*R*)-2-hydroxy-1-methylethyl]benzenesulfonamide;
- 4-Bromo-N-[(1*R*)-2-methoxy-1-methylethyl]benzenesulfonamide;
- 4-Bromo-N-[(1*S*)-2-methoxy-1-methylethyl]benzenesulfonamide;
- Methyl 3-amino-6-[4-(pyrrolidin-1-ylsulfonyl)phenyl]pyrazine-2-carboxylate;
- 45 4-[(4-Methylpiperazin-1-yl)sulfonyl]phenylboronic acid;

PRU/M/2-12-17

Methyl 3-amino-6-[4-[(4-methyl-1-piperazinyl)sulfonyl]phenyl]pyrazine-2-carboxylate;

3-Amino-6-[4-[(4-methyl-1-piperazinyl)sulfonyl]phenyl]-2-pyrazinecarboxylic acid;

5 4-[2-(4-Bromo-2-fluorophenoxy)ethyl]morpholine;

4-Bromo-N-(1-ethyl-3-piperidinyl)benzenesulfonamide;

4-Bromo-N,N-bis(2-methoxyethyl)benzenesulfonamide;

10 4-bromo-N-(3-methylbutyl)-benzenesulfonamide;

Methyl 3-[(2,6-dimethoxy-4-(2-phenylethoxy)benzyl]amino}-6-[4-(pyrrolidin-1-ylsulfonyl)phenyl]pyrazine-2-carboxylate polystyrene;

15 3-[(2,6-Dimethoxy-4-(2-phenylethoxy)benzyl]amino}-6-[4-(pyrrolidin-1-ylsulfonyl)phenyl]pyrazine-2-carboxylic acid polystyrene;

20 4-{5-Amino-6-[(pyridin-3-ylamino)carbonyl]pyrazin-2-yl}benzoic acid;

as a free base or a salt, solvate or solvate of a salt thereof.

25 Listed below are definitions of various terms used in the specification and claims to describe the present invention.

For the avoidance of doubt it is to be understood that where in this specification a group is qualified by 'hereinbefore defined', 'defined hereinbefore', 'is as defined above' or 'are as defined above' the said group encompasses the first occurring and broadest definition as well as each and all of the preferred definitions for that group.

30 For the avoidance of doubt it is to be understood that in this specification 'C₀₋₆' means a carbon group having 0, 1, 2, 3, 4, 5 or 6 carbon atoms.

35 In this specification, unless stated otherwise, the term "alkyl" includes both straight and branched chain alkyl groups. C₁₋₆alkyl may be methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, t-pentyl, neo-pentyl, hexyl.

The term "alkoxy" as used herein, unless stated otherwise includes "alkyl"O groups in which "alkyl" is as hereinbefore defined. C₁₋₅alkoxy may be methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, n-pentyloxy, i-pentyloxy, t-pentyloxy, neo-pentyloxy.

5 In this specification, unless stated otherwise, the term "5 or 6 membered heteroaromatic ring containing one or more heteroatoms independently selected from N, O, or S" may be, but are not limited to, furyl, isoxazolyl, isothiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, thiazolyl, thienyl or imidazolyl.

10 In this specification, unless stated otherwise, the term "5 or 6 membered heterocyclic ring containing one or more heteroatoms independently selected from N, O, or S" may be, but are not limited to, imidazolidinyl, imidazolinyl, morpholinyl, piperazinyl, piperidyl, piperidonyl, pyrazolidinyl, pyrazolinyl, pyrrolidinyl, pyrrolinyl, tetrahydropyranyl or 15 thiomorpholinyl.

In this specification, unless stated otherwise, the term halogeno may be fluorine, chlorine, bromine or iodine.

20 The present invention relates to the use of compounds of formula I as hereinbefore defined as well as to the salts, solvates and solvates of salts thereof. Salts for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of formula I.

25 Both organic and inorganic acids can be employed to form non-toxic pharmaceutically acceptable acid addition salts of the compounds, e.g. hydrochlorides of this invention. In addition, a suitable pharmaceutically acceptable salt of the compounds of the invention, which is sufficiently acidic is an alkali metal salt, an alkaline earth metal salt or a salt with an organic base, which affords a physiologically-acceptable cation.

PRU02-12-17

10-

Some compounds of formula I may have chiral centres and/or geometric isomeric centres (E- and Z- isomers), and it is to be understood that the invention encompasses all such diastereoisomers, optical and geometric isomers that possess GSK3 inhibitory activity.

- 5 It is to be understood that the present invention relates to any and all tautomeric forms of the compounds of formula I.

An object of the invention is to provide compounds of formula I for therapeutic use, especially compounds that are useful for the prevention and/or treatment of
10 conditions associated with glycogen synthase kinase-3 (GSK3) in mammals including man. Particularly, compounds of formula I exhibiting a selective affinity for GSK-3.

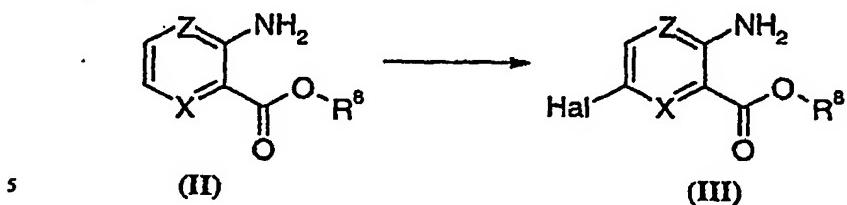
15 It is also an object of the invention to provide compounds with a therapeutic effect after oral administration.

METHODS OF PREPARATION

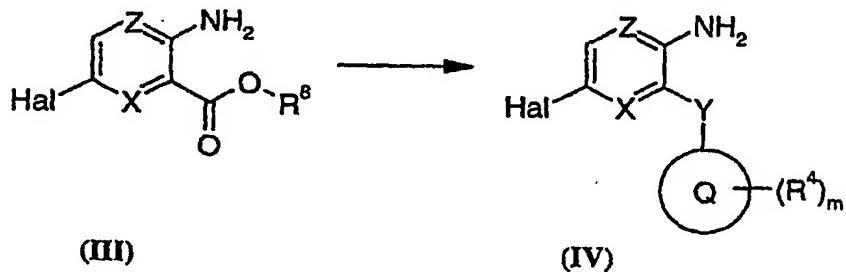
20 Another aspect of the present invention provides a process for preparing a compound of formula I as a free base or a pharmaceutically acceptable salt thereof. Throughout the following description of such processes it is understood that, where appropriate, suitable protecting groups will be added to, and subsequently removed from, the various reactants and intermediates in a manner that will be readily understood by one skilled in the art of organic synthesis. Conventional procedures for using such protecting groups as well as examples of suitable protecting groups are described, for example, in
25 "Protective Groups in Organic Synthesis" T.W. Green, P.G.M. Wuts, Wiley-Interscience, New York, 1999.

Methods of preparation of intermediates

The process for the preparation of the intermediates, wherein Y, X, Z, P, Q, R, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹² A, m and n are, unless specified otherwise, defined as in formula I, comprises of:



- (i) halogenation of a compound of formula II, wherein X and Z are N, R⁸ is hydrogen, C₁-alkyl or when R⁸ is hydrogen in the form of a salt such as a sodium salt, to obtain a compound of formula III, may be carried out using a suitable halogenating reagent e.g. iodine, bromine, chlorine, halide salts for example ICl, BrCl or HOCl or other suitable halogenation reagents e.g. *N*-bromosuccinimide or phosphorous tribromide. The reaction may be catalysed by metals or acids such as Fe, Cu-salts, acetic acid or sulfuric acid or aided by oxidising agents e.g. nitric acid, hydrogen peroxide or sulfur trioxide. The reaction may be carried out in a suitable solvent such as water, acetic acid or chloroform at a temperature in the range of -70 °C to +100 °C.

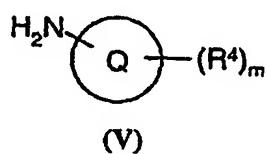


- (ii) amidation of a compound of formula III, wherein X and Z are N, R⁸ is C₁₋₆alkyl to obtain a compound of formula IV, wherein Y is CONR⁵ and R⁴, Q and m are as defined above may be carried out by treating a compound of formula III with the

PROJ002-12-17

12

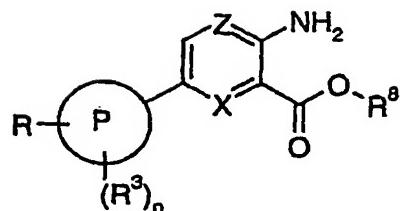
appropriate amine such as a compound of formula V, wherein Q is phenyl, wherein R⁴ and m are as defined above, or a 5 or 6 membered heteroaromatic ring containing one or more heteroatoms selected from N, O or S. The reaction may be performed neat or using a suitable solvent such as N,N-dimethylformamide, methylene chloride or ethyl acetate at a temperature ranging from -25 °C to +150 °C. The reaction may be aided by using a base such as potassium carbonate, triethylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene or an acid such as trimethylaluminum or p-toluenesulfonic acid.



10

(iii) amidation of a compound of formula III, wherein R⁸ is hydrogen, to obtain a compound of formula IV, wherein Y is CONR⁵, m are as defined above, and R⁴ is a substituent that is not susceptible to certain coupling agents, may be performed by activation of a compound of formula III by treating the compound with coupling reagents such as 1,3-diisopropylcarbodiimide, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, 1,3-dicyclohexylcarbodiimide, O-(benzotriazol-1-yl)-N, N, N', N'-tetramethyluronium tetrafluoroborate, O-(benzotriazol-1-yl)-N, N, N', N'-tetramethyluronium hexafluorophosphate, 1,1'-carbonyldimidazole or O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate where the reaction may be aided by the addition of 1-hydroxybenzotriazole hydrate, or using an acyl halide reagent such as cyanuric chloride, oxalyl chloride, thionyl chloride or bromotrispyrrolidinophosphonium hexafluorophosphate, followed by treatment with the appropriate amine such as a compound of formula V in a suitable solvent such as methylene chloride chloroform, acetonitrile or tetrahydrofuran and at a reaction temperature between 0 °C and reflux. The reaction may be aided by using a base such as potassium carbonate or a trialkylamine e.g triethylamine or N-ethyl-N,N-diisopropylamine

30



(iv) conversion of a compound of formula III to a compound of formula VI, wherein X and Z are N, R⁸ is C₁-6alkyl and R, R³, P and n are as defined above, may be carried out by a de-halogen coupling with a suitable compound of formula XVIIa-c

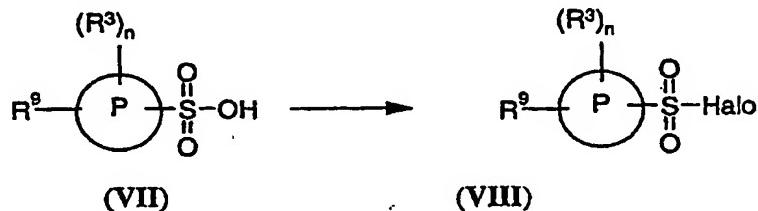
The reaction may be carried out by coupling of a compound of formula III with an appropriate aryl boronic acid or a boronic ester of formula XVIIa-c (the boronic acid or boronic ester may be formed in situ using the compounds of formula XI, XIII, XV or XXI and conditions described in (xii)). The reaction may be carried out using a suitable palladium catalyst such as Pd(PPh₃)₄, Pd(dppf)Cl₂ or Pd(OAc)₂ with or without a suitable ligand such as P(*tert*-butyl)₃ or 2-(dicyclohexylphosphino)biphenyl in the presence of a suitable base such as an alkylamine e.g. triethylamine, or potassium carbonate, potassium phosphate, sodium carbonate, sodium hydroxide or cesium fluoride, or a nickel catalyst such as nickel on charcoal or Ni(dppe)Cl₂ together with Zn and sodium triphenylphosphine trimetasulfonate. A suitable base such as an alkylamine e.g. triethylamine, or potassium carbonate, potassium phosphate, sodium carbonate, sodium hydroxide or cesium fluoride may be used in the reaction, which reactions are performed in a temperature range between +20 °C and +160 °C using an oil bath or a microwave oven in a suitable solvent such as ethanol, water, toluene, tetrahydrofuran, dimethoxyethane or *N,N*-dimethylformamide or mixtures thereof.

25

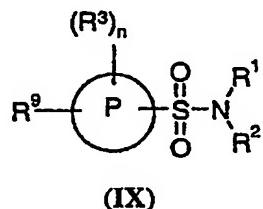
(v) conversion of a compound of formula VI, wherein R⁸ is C₁-6alkyl, to a compound of formula VI, wherein R⁸ is hydrogen, may be carried out in a suitable solvent such as

PRU02-12-17

tetrahydrofuran or water or mixtures thereof in the presence of a suitable base such as potassium carbonate, sodium hydroxide or lithium hydroxide at a reaction temperature between +20 °C and +60 °C.

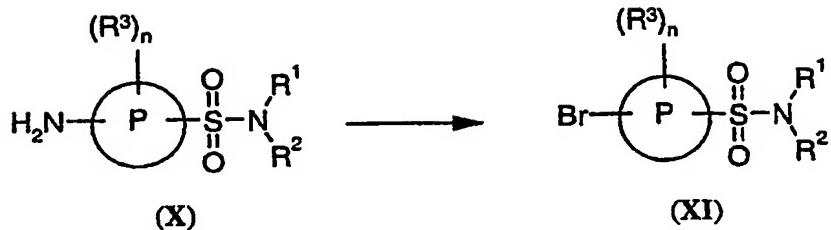


- (vi) halogenating a compound of formula VII, wherein R⁹ is bromine or NH₂ and P, R³ and n are as defined above, to obtain a compound of formula VIII may be carried out by treatment of a compound of formula VII with a halogenation reagents such as thionyl chloride or oxalyl chloride. The reaction may be performed neat or in a suitable solvent such as tetrahydrofuran, dioxane or methylene chloride at a temperature range between -20 °C and +60°C;



- (vii) amidation of a compound of formula VIII, wherein R⁹ is bromine or NH₂, halo is fluorine, chlorine or bromine and P, R³ and n are as defined above, to obtain a compound of formula IX, wherein R⁹ is bromine or NH₂ and P, R¹, R², R³ and n are as defined above,
20 may be carried out by reacting a compound of formula VIII with the suitable amine HNR¹R². The reaction may be performed in a suitable solvent such as tetrahydrofuran, dioxane, N,N-dimethylformamide or methylene chloride with or without a suitable base such as a trialkylamine e.g. triethylamine, or potassium carbonate, sodium hydroxide or sodium hydrogen carbonate in a temperature range between 0 °C and +50 °C.

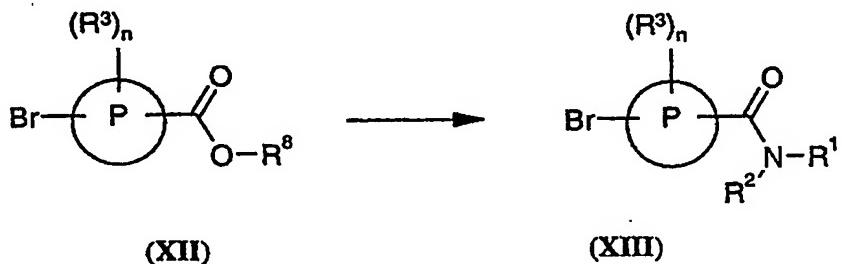
5



10

(viii) conversion of a compound of formula **X** to obtain a compound of formula **XI**, wherein R^1 , R^2 , R^3 , n and P are as defined above, may be carried out by treatment of a compound of formula **X** with sodium nitrite and hydrobromic acid followed by the addition of a bromide source such as CuBr in an appropriate solvent such as water at a temperature range between $0\text{ }^\circ\text{C}$ and $+5\text{ }^\circ\text{C}$.

15



20

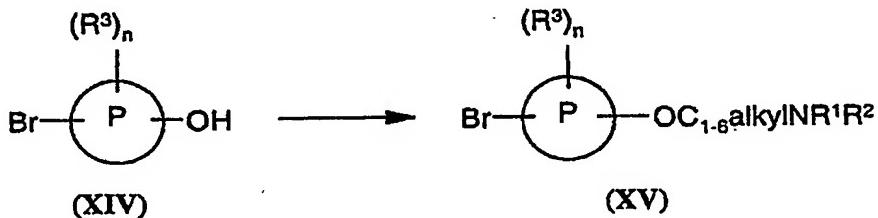
(ix) formation of an amide of formula **XIII**, wherein R^1 , R^2 , R^3 , n and P are as defined above, may be carried out by treating a compound of formula **XII**, wherein R^8 is $\text{C}_{1-6}\text{alkyl}$, with the appropriate amine HNR^1R^2 . The reaction can be performed neat or using a suitable solvent such as N,N -dimethylformamide, methylene chloride or ethyl acetate at a temperature ranging from $-25\text{ }^\circ\text{C}$ to $+150\text{ }^\circ\text{C}$. The reaction may be aided by using a base such as potassium carbonate, triethylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene or an acid such as trimethylaluminum or p-toluenesulfonic acid.

25

(x) amidation of a compound of formula **XII**, wherein R^8 is hydrogen and R^3 , n and P are as defined above to obtain a compound of formula **XIII** may be performed by activation of

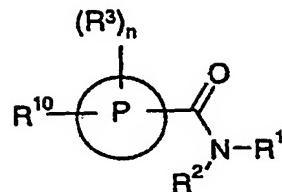
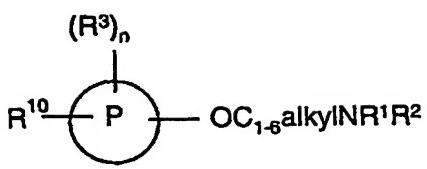
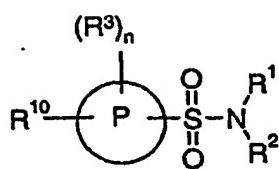
a compound of formula XII by treating the compound with coupling reagents such as 1,3-diisopropylcarbodiimide, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, 1,3-dicyclohexylcarbodiimide, O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate, O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, 1,1'-carbonyldiimidazole or O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate where the reaction may be aided by the addition of 1-hydroxybenzotriazole hydrate, or using an acyl halide reagent such as cyanuric chloride, oxalyl chloride, thionyl chloride or bromotrispyrrolidinophosphonium hexafluorophosphate, followed by treatment with the appropriate amine HNR¹R². The reaction may be carried out in a suitable solvent such as N,N-dimethylformamide, acetonitrile or methylene chloride at a temperature ranging from -25 °C to +150 °C, with or without a suitable base such as an alkylamine e.g. triethylamine, N-ethyl-N,N-diisopropylamine or N-methylmorpholine, or potassium carbonate or sodium hydroxide.

15



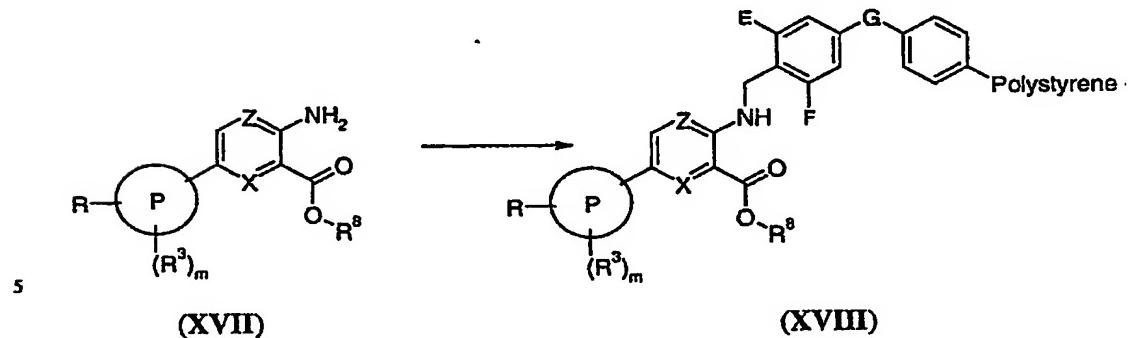
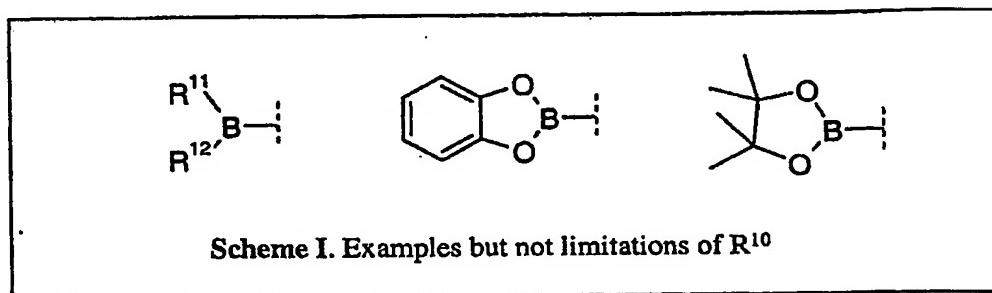
(xi) conversion of a compound of formula XIV, wherein R³, n and P are as defined above,
20 to obtain a compound of formula XV, wherein R¹, R², R³, n, C₁₋₆alkyl and P are as defined
above, may be carried out by reacting a compound of formula XIV with a suitable alcohol,
R¹R²NC₁₋₆alkylOH in the presence of triphenylphosphine and an appropriate
azidodicarboxylate such as diethyl azidodicarboxylate. The reaction may be performed in a
suitable solvent such as tetrahydrofuran, toluene or methylene chloride and at a reaction
25 temperature between 0 °C to 60 °C.

5

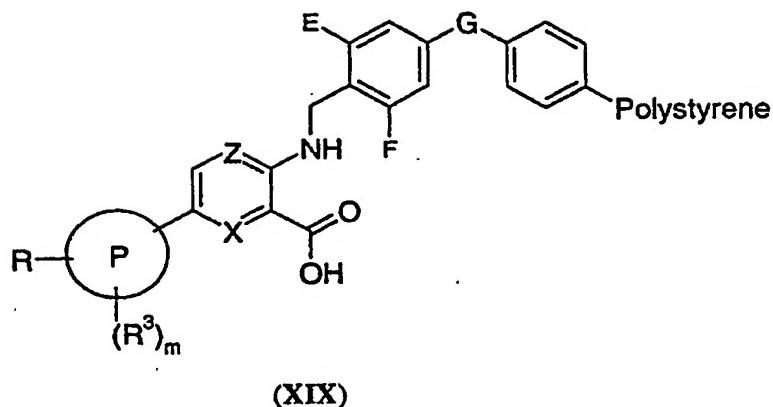


- 10 (xii) borylation of compounds of formula **XI**, **XIII** and **XV** to compounds of formula **XVIa-c** (**XVIa** from **XI**, **XVIb** from **XV** and **XVI** from **XIII**), wherein P, R¹, R², R³, C₁-alkyl and n are as defined above and R¹⁰ may be a group outlined in Scheme I, wherein R¹¹ and R¹² are C₁₋₆alkoxy or hydroxy, or C₁₋₃alkoxy fused together to form a 5 or 6 membered cyclic boron-oxygen-C₂₋₃alkyl species and the alkoxy, the aryl group or 5 or 6 membered cyclic boron-oxygen-C₂₋₃alkyl species may be optionally substituted, may be carried out by a reaction with:
- 15 a) butyllithium or magnesium and a suitable boron compound such as trimethyl borate or triisopropyl borate. The reaction may be performed in a suitable solvent such as tetrahydrofuran, hexane or methylene chloride in a temperature range between -78 °C and +20 °C;
- 20 or,
- b) a palladium catalyst such as palladium tetrakis(triphenylphosphine), palladium diphenylphosphineferrocene dichloride or palladium acetate with or without a suitable ligand such as 2-(dicyclohexylphosphino)biphenyl, and a suitable boron species such as bis(catecholato)diboron, bis(pinacolato)diboron or pinacolborane. A suitable base, which under the reaction conditions do not promote dimerisation of compounds of formula **XI**, **XIII** and **XV**, such as a tertiary amine such as triethylamine or diisopropylethylamine or

potassium acetate may be used. The reaction may be performed in a solvent such as dioxane, toluene or acetonitrile at temperatures between +80 °C and +100 °C.

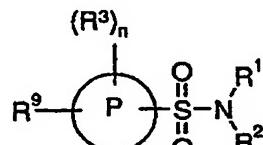


(xiii) conversion of a compound of formula XVII, wherein R⁸ is C₁₋₆alkyl and R, R³, N, X, Z and m are as defined above, to a compound of formula XVIII, wherein E and F are a methoxy group or hydrogen and G is a spacer chain containing atoms selected from O and C, may be carried out by reaction with a suitable solid phase reagent such as a formyl polystyrene e.g. 2-(3,5-dimethoxy-4-formylphenoxy)ethyl polystyrene or 2-(4-formyl-3-methoxyphenoxy)ethyl polystyrene in a suitable solvents such as N,N-dimethylformamide or methylene chloride in the presence of a suitable acid e.g. acetic acid and a suitable reducing reagent such as sodium triacetoxyborohydride or sodium cyanoborohydride at a suitable reaction temperature ranging between 0 °C and +50 °C. The reaction may be aided by the presence of trimethylsilyl chloride.



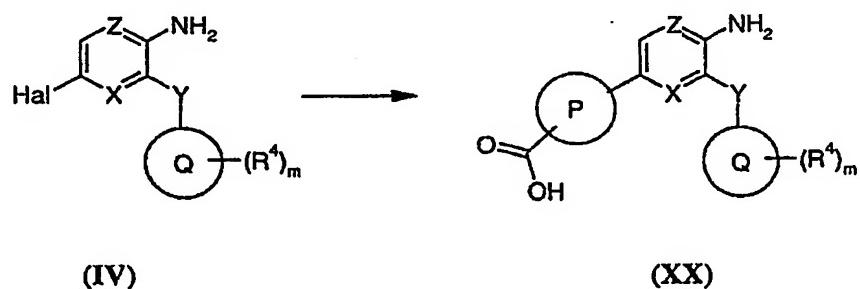
(xiv) hydrolysis of a compound of formula XVIII, wherein R, R³, N, X, Z, E, F, G and m are as defined above, to a compound of formula XIX may be carried out in a suitable

s solvent such as water, tetrahydrofuran or mixtures thereof in the presence of a suitable base such as sodium hydroxide, potassium hydroxide or lithium hydroxide at a suitable reaction temperature ranging between +25 °C and reflux.

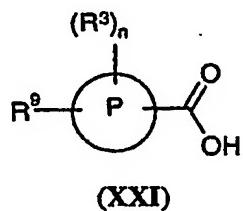


(IX)

10 (xv) conversion of a compound of formula IX, wherein R¹, R³, R⁹, P and n are as defined above and R² is C₁₋₆alkylOR⁶ and R⁶ is hydrogen, to a compound of formula IX, wherein R¹, R³, R⁹, P and n are as defined above and R² is C₁₋₆alkylOR⁶ and R⁶ is C₁₋₆alkyl, may be carried out in a suitable solvent such as methylene chloride or chloroform using a suitable reagent such as (trimethylsilyl)diazomethane in a reaction temperature between 0 °C and 15 20 °C. The reaction may be aided by the use of a reagent such as fluoroboric acid.



(xvi) conversion of a compound of formula IV, wherein Z, X, Q, R⁴ and m are as defined above, to a compound of formula XX, wherein Z, X, Q, R⁴ and m are as defined above, may be carried out by the method described in (iv) using a compound of formula XXI, wherein P, R³, R⁹ and n are as defined above.

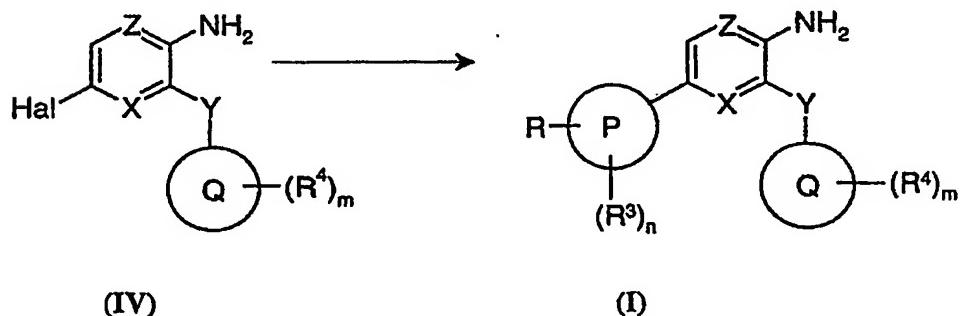


10 Methods of preparation of the end products

Another object of the invention are processes for the preparation of a compound of general formula I, wherein Y, X, Z, P, Q, R, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, A, m and n are, unless specified otherwise, defined as in formula I, comprising of:

15 A

De-halogen coupling, wherein R³ and R⁴ are substituents that are not susceptible to certain agents in the reaction, of a compound of formula IV with a appropriate aryl species to give a compound of formula I:



Thus, the de-halogen coupling according to process A may be carried out by coupling of a compound of formula IV with:

- a) an appropriate aryl halogen such as aryl iodide, aryl bromide or aryl chloride in the presence of metals such as copper, nickel or zink and nickel complexes, copper oxide or palladium acetate and tetrabutylammonium bromide and a base such as potassium carbonate or triethylamine. The reaction may occur at a temperature between 20 °C and 180 °C in a suitable solvent such as *N,N*-dimethylformamide, toluene or 2-pentanol; or,
- b) an appropriate aryl boronic acid or a boronic ester such as compounds of formula XVIa-c (the boronic acid or boronic ester may be formed in situ using the compounds of formula XI, XIII and XV and conditions described in (xii)). The reaction may be carried out using a suitable palladium catalyst such as Pd(PPh₃)₄, Pd(dppf)Cl₂ or Pd(OAc)₂ with or without a suitable ligand such as P(*tert*-butyl)₃ in the presence of a suitable base such as an alkylamine e.g. triethylamine, or potassium carbonate, sodium carbonate, sodium hydroxide or cesium fluoride, which is performed in a temperature range between +20 °C and +160 °C using an oil bath or a microwave oven in a suitable solvent or solvent mixture such as toluene, tetrahydrofuran, ethylene glycol dimethyl ether/water, dimethoxyethane/water or *N,N*-dimethylformamide.
- or,
- 2-(dicyclohexylphosphino)biphenyl or a nickel catalyst such as nickel on charcoal or Ni(dppe)Cl₂ together with Zn and sodium triphenylphosphinetrimetasulfonate. A suitable base such as an alkylamine e.g. triethylamine, or potassium carbonate, sodium carbonate, sodium hydroxide or cesium fluoride may be used in the reaction, which is performed in the temperature range between +20 °C and +160 °C using an oil bath or in a microwave oven in a suitable solvent or solvent mixture such as toluene, tetrahydrofuran, tetrahydrofuran/water, dimethoxyethane/water or *N,N*-dimethylformamide;
- or,
- c) an appropriate aryl stannane in the presence of palladium catalyst such as Pd(PPh₃)₄, Pd(PPh₃)₂Cl₂ or Pd(dba)₃ and if needed a helping reagent such as 4-*tert*-butylcatechole, lithium chloride or potassium carbonate. Suitable solvents may be toluene, tetrahydrofuran

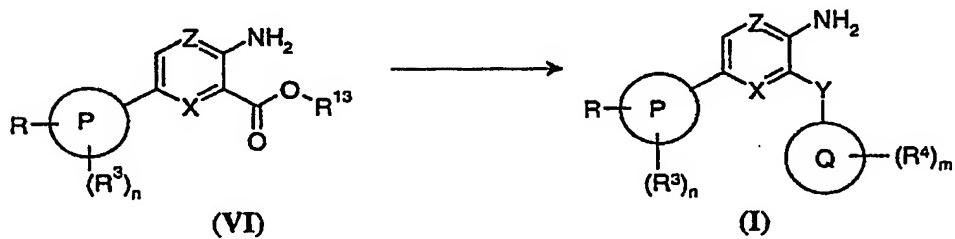
or *N,N*-dimethylformamide. The reaction may occur in a temperature range of +20 °C and +120 °C;

or,

- d) an appropriate aryl halogen such as aryl iodide or aryl bromide by treatment with butyllithium in a suitable solvent such as tetrahydrofuran at a reaction temperature between -78 °C and -25 °C, and a suitable base such as sodium carbonate or potassium carbonate in the presence of a suitable palladium catalyst such as Pd(dppf)Cl₂ or Pd(OAc)₂ and at a reaction temperature between 25 °C and reflux.

10 . B

Amidation, wherein R³ and R⁴ are substituents that are not susceptible to certain agents in the reaction, of a compound of formula VI with the appropriate amine:



15

Thus, the amidation according to process B may be carried out by treating a compound of formula VI, wherein R⁸ is C₁-C₆alkyl, with the appropriate amine such as a compound of formula V. The reaction can be performed neat or using a suitable solvent such as N,N-dimethylformamide, acetonitrile, methylene chloride or ethyl acetate at a temperature ranging from -25 °C to +150 °C. The reaction may be aided by using a base such as potassium carbonate, triethylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene or an acid such as trimethylaluminum or p-toluenesulfonic acid;

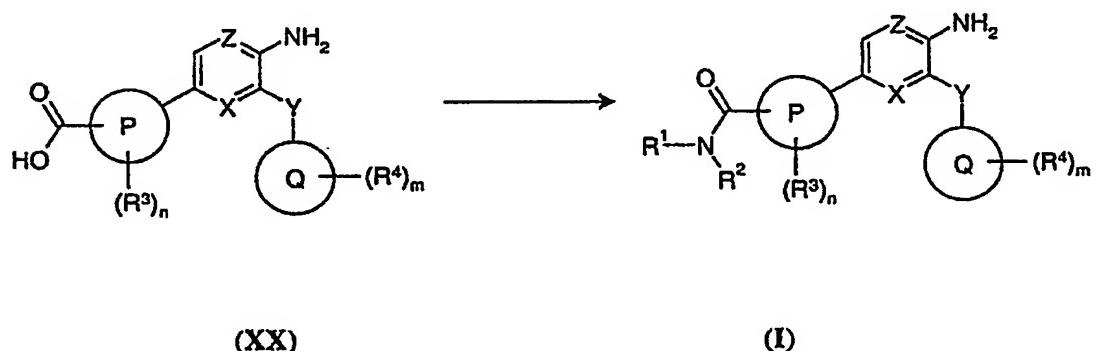
or,

the amidation of a compound of formula VI, wherein R⁸ is hydrogen, may be performed by activation of a compound of formula VI by treating the compound with coupling reagents such as 1,3-diisopropylcarbodiimide, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, 1,3-dicyclohexylcarbodiimide, O-(benzotriazol-1-yl)-N, N, N', N'-tetramethyluronium tetrafluoroborate, O-(benzotriazol-1-yl)-N, N, N', N'-

tetramethyluronium hexafluorophosphate, 1,1'-carbonyldiimidazole or *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate where the reaction may be aided by the addition of 1-hydroxybenzotriazole hydrate, or using an acyl halide reagent such as cyanuric chloride, oxalyl chloride, thionyl chloride or bromotrispyrrolidinophosphonium hexafluorophosphate followed by treatment with the appropriate amine such as a compound of formula V in a suitable solvent such as methylene chloride chloroform, *N,N*-dimethylformamide, acetonitrile, tetrahydrofuran or mixtures thereof and at a reaction temperature between 0 °C and reflux. The reaction may be aided by using a base such as potassium carbonate or a trialkylamine e.g triethylamine or *N*-ethyl-*N,N*-diisopropylamine

C

Amidation, wherein R³ and R⁴ are substituents that are not susceptible to certain agents in the reaction, of a compound of formula XX, with the appropriate amine to give a compound of formula I:



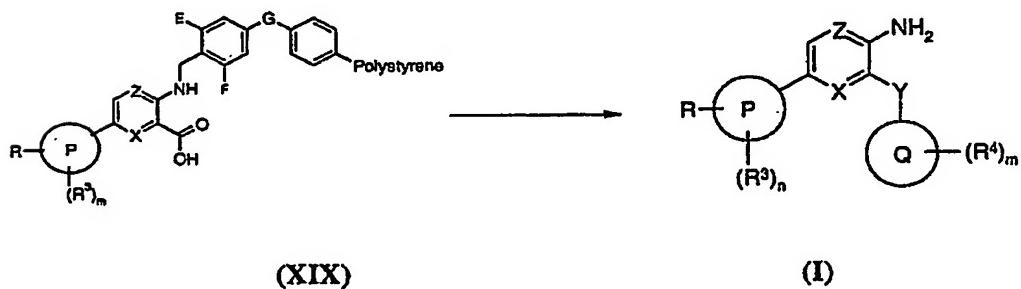
25 Thus the amidation of a compound of formula I according to process C may be performed by activation of the carboxylic acid function in a compound of formula XX, wherein R is COOH, by treating the compound with coupling reagents such as 1,3-diisopropylcarbodiimide, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, 1,3-dicyclohexylcarbodiimide, O-(benzotriazol-1-yl)-N, N, N', N'-tetramethyluronium

tetrafluoroborate, O-(benzotriazol-1-yl)-N, N, N', N'-tetramethyluronium hexafluorophosphate, 1,1'-carbonyldiimidazole or O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate where the reaction may be aided by the addition of 1-hydroxybenzotriazole hydrate, or using an acyl halide reagent such as cyanuric chloride, oxalyl chloride, thionyl chloride or bromotrispyrrolidinophosphonium hexafluorophosphate in a suitable solvent such as N,N-dimethylformamide, methylene chloride, methanol, dioxane or tetrahydrofuran followed by treatment with the appropriate amine HNR¹R² and at a reaction temperature between 25 °C and 70 °C.

10 D

Amidation, wherein R³ and R⁴ are substituents that are not susceptible to certain agents in the reaction, of a compound of formula XIX with the appropriate amine:

15



Thus, the amidation of a compound of formula **XIX**, may be performed by activation of a compound of formula **XIX** by treating the compound with coupling reagents such as 1,3-diisopropylcarbodiimide, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, 1,3-dicyclohexylcarbodiimide, O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate, O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, 1,1'-carbonyldiimidazole or O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate where the reaction may be aided by the addition of 1-hydroxybenzotriazole hydrate, or using an acyl halide reagent such as cyanuric

chloride, oxalyl chloride, thionyl chloride or bromotrispyrrolidinophosphonium hexafluorophosphate followed by treatment with the appropriate amine such as a compound of formula V in a suitable solvent such as methylene chloride chloroform, N,N-dimethylformamide, acetonitrile or tetrahydrofuran and at a reaction temperature between 5 0 °C and reflux. The reaction may be aided by using a base such as potassium carbonate or a trialkylamine e.g triethylamine or N-ethyl-N,N-diisopropylamine, followed by, cleavage of the solid phase moiety by treatment with an suitable acid such as trifluoroacetic acid in a suitable solvent such as methylene chloride or chloroform and at a reaction temperature between 0 °C and reflux to give the compound of formula (I).

The hydrochloric salt of compound of formula I may be obtained from a compound of formula I by treatment with hydrochloric acid at a temperature range between 0 °C and +25 °C, in suitable solvent such as methylene chloride, tetrahydrofuran or methylene chloride/methanol mixture.

WORKING EXAMPLES

20 **Example 1**
 3-Amino-6-bromo-N-pyridin-3-ylpyrazine-2-carboxamide
 To 3-aminopyridine (10 g, 106 mmol) at 70 °C were added methyl 3-amino-6-bromo-2-pyrazinecarboxylate (1.0 g, 4.3 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (645 µL, 4.3 mmol). The reaction solution was stirred for 4 h, diluted with water (75 mL) and extracted with methylene chloride. The combined organic layers were washed with a saturated ammonium chloride solution, dried (MgSO_4), filtered and evaporated in vacuo. The crude product was purified on a silica gel column using methylene chloride/ethanol, (9:1), as the eluent to give 750 mg (59% yield) of the title compound as a yellow solid: ^1H NMR (CDCl_3 , 400 MHz) δ 9.50 (br s, 1 H), 8.82 (d, J = 3 Hz, 1 H), 8.43 (dd, J = 5 and 1 Hz, 1 H), 8.31 (s, 1 H), 8.23 (ddd, J = 8, 3 and 2 Hz, 1 H), 7.34 (dd, J = 8, 5 Hz, 1 H); MS (TSP) m/z 294 (M^++1).

Example 2**1-[(4-Bromophenyl)sulfonyl]pyrrolidine**

Pyrrolidine (2.5 g, 35.2 mmol) was added to a solution of 4-bromobenzenesulfonyl chloride 4.5 g, 17.6 mmol) in methylene chloride (10 mL) at 0 °C. The mixture was stirred for 2 h and an aqueous sodium hydroxide solution (1 M, 5 mL) was added and stirring was continued for another 10 min. The organic phase was separated and diluted with methylene chloride (40 mL), washed with aqueous HCl (1 M, 10 mL), and water (2x10 mL). The organic phase was dried (sodium sulfate) and the solvent was evaporated. The title compound was isolated in 5.0 g (98% yield) as a white solid: ^1H NMR (CDCl_3 , 400 MHz) δ 7.65 (m, 4 H), 3.20 (m, 4 H), 1.74 (m, 4 H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 135.93, 132.17, 128.84, 127.39, 47.84, 25.13; MS (ES) m/z 290 and 292 (M^++1).

Example 3**4-(Pyrrolidin-1-ylsulfonyl)phenylboronic acid**

n-Butyllithium (20 mL, 31 mmol) was added dropwise over 30 min to a cooled (-78 °C) solution of 1-(4-bromobenzenesulfonyl)pyrrolidine (3.0 g, 10.3 mmol) and triisopropyl borate (7.2 mL, 30.9 mol) in anhydrous tetrahydrofuran (10 mL) under a nitrogen atmosphere. The reaction mixture was stirred for 1 h at -78 °C whereafter the temperature was allowed to reach room temperature over 3 h. Silica gel was added and the solvent was evaporated. Chromatography on a silica gel column using a gradient methylene chloride (100%) to methylene chloride/ethanol, (1:1), gave 1.85 g (70% yield) of the title compound as a white solid: ^1H NMR (CD_3OD , 400 MHz) δ 7.90 (d, $J = 7$ Hz, 2 H), 7.75 (d, $J = 8$ Hz, 2 H), 3.21 (m, 4 H), 1.72 (m, 4 H); ^{13}C NMR ($\text{CDCl}_3/\text{CD}_3\text{OD}$ (1:1), 100 MHz) δ 136.79, 133.50, 125.48, 47.19, 24.30; MS (ES) m/z 256 (M^++1).

Example 4**4-Bromo-N-[(1*R*)-2-hydroxy-1-methylethyl]benzenesulfonamide**

(2*R*)-2-Aminopropan-1-ol (2.0 g, 26.7 mmol) and *N*-ethyl-*N,N*-diisopropylamine (8.5 mL, 48.9 mmol) was added dropwise over 20 min to a cooled (0 °C) solution of 4-bromobenzenesulfonyl chloride (6.12 g, 24 mmol) in methylene chloride (20 mL). The reaction mixture was allowed to stir for 1 h. Water was added and the mixture was washed,

twice, with HCl (aq, 1 M) and one time with saturated aqueous sodium hydrogen carbonate. The organic phase was dried over sodium sulfate and evaporated to give 6.8 g, (96% yield) of the title compound: ^1H NMR (CD_3OD , 400 MHz) δ 7.82 (d, $J = 8$ Hz, 2 H), 7.76 (d, $J = 8$ Hz, 2 H), 3.44 (m, 1 H), 3.34 (m, 3 H), 1.03 (d, $J = 7$ Hz, 3 H); MS (ESI) m/z ($M^+ + 1$); ^{13}C NMR (CD_3OD , 100 MHz) 142.42, 133.36, 129.74, 127.90, 66.81, 52.49, 17.94

Example 5

4-Bromo-N-[(1*R*)-2-methoxy-1-methylethyl]benzenesulfonamide

(Trimethylsilyl)diazomethane (10 mL, 10 mmol) was added to a vigorously stirred mixture of 4-bromo-N-[(1*R*)-2-hydroxy-1-methylethyl]benzenesulfonamide (1.0 g, 3.4 mmol) and aqueous fluoroboric acid (conc. 42%, 6.8 mmol) in methylene chloride (25 mL), in 5 portions over 1 h at 0 °C. The stirring was continued at 0 °C and another portion of trimethylsilyldiazomethane (5 mL, 5 mmol) was added over 30 min. The stirring was continued for 30 min, poured into water and extracted with methylene chloride. The organic phase was washed with water, dried over sodium sulfate and concentrated. Purification by column chromatography using gradient heptane to heptane/ethylacetate, (2:1), as the eluent gave 0.155 g (15% yield) of the title compound: MS (ESI) 309 m/z ($M^+ + 1$).

20

Example 6

4-Bromo-N-[(1*S*)-2-methoxy-1-methylethyl]benzenesulfonamide

(1*S*)-2-Methoxy-1-methylethylamine (7.34 g, 82.4 mmol) and *N*-ethyl-*N,N*-diisopropylamine (19.1, 110 mmol) was added dropwise over 20 min to a cooled (0 °C) solution of 4-bromobenzenesulfonyl chloride (14.0 g, 55 mmol) in methylene chloride (200 mL). The reaction mixture was allowed to stir for 1 h. Water was added and the mixture was washed, twice, with HCl (1 M) and once with saturated aqueous sodium hydrogen carbonate. The organic phase was dried over sodium sulfate and evaporated to give 15.1 g, (94% yield) of the title compound: ^1H NMR (CDCl_3 , 400 MHz) δ 7.76 (d, $J = 8$ Hz, 2 H), 7.65 (d, $J = 8$ Hz, 2 H), 4.97 (m, 1 H), 3.46 (m, 1 H), 3.23 (m, 5 H), 1.12 (d, $J = 7$ Hz, 3 H); MS (ESI) m/z 308 and 310 ($M^+ + 1$)

PPN/AD2-12-17

Example 7

Methyl 3-amino-6-[4-(pyrrolidin-1-ylsulfonyl)phenyl]pyrazine-2-carboxylate

4-(Pyrrolidin-1-ylsulfonyl)phenylboronic acid (0.33 g, 1.29 mmol), methyl 3-amino-6-bromopyrazine-2-carboxylate (0.25 g, 1.08 mmol), K_3PO_4 (3 M, 1.1 mL, 3.2 mmol), and Pd(dppf)Cl₂ (0.044 g, 54 μ mol) were suspended in ethylene glycol/dimethyl ether/water (1.5:0.5 mL) and heated in a microwave oven at 160 °C for 10 min. The reaction was repeated 3 times. The combined product mixtures were evaporated with silica gel and the crude product was purified by chromatography on silica gel using a heptane to ethyl acetate gradient to give 0.96 g (82% yield) of the title compound: MS (ES) *m/z* 363 (M^++1).

Example 8**4-[(4-Methylpiperazin-1-yl)sulfonyl]phenylboronic acid**

Triisopropyl borate (0.64 mL, 2.8 mmol) was added to a solution of 1-[(4-bromophenyl)sulfonyl]-4-methylpiperazine (0.602 g, 1.9 mmol; described: in Keasling, H. H. et al. *J. Med. Chem.* 1965, 8, 548-550) in anhydrous tetrahydrofuran (7 mL) at -78 °C under a nitrogen atmosphere followed by dropwise addition of *n*-butyllithium (1.4 mL, 2.2 mmol). The resulting mixture was stirred at -78 °C for 2 h and at room temperature for another 16 h. Water (2.0 mL) was added and the mixture stirred for 30 min and evaporated to dryness. The residue was pre-adsorbed onto silica and purified by column chromatography using methylene chloride/methanol, (9:1 to 1:9), as the eluent. The product was re-crystallized from water to give 311 mg (58% yield) of the title compound as white crystals: mp 215-218 °C; ¹H NMR (DMSO-d₆, 400 MHz) δ 10.89 (br s, 1 H), 8.47 (br s, 2 H), 8.05 (d, *J* = 8 Hz, 2 H), 7.73 (d, *J* = 8 Hz, 2 H), 3.77 (m, 2 H), 3.40 (m, 2 H), 3.13 (m, 2 H), 2.71 (s, 3 H), 2.65 (m, 2 H); ¹³C NMR (DMSO-d₆, 100 MHz) δ 133.7, 133.3, 124.7, 49.8, 41.6, 41.4; MS (TSP) *m/z* 285 (M^++1).

Example 9**Methyl 3-amino-6-[4-[(4-methyl-1-piperazinyl)sulfonyl]phenyl]pyrazine-2-carboxylate**

Triisopropyl borate (2.7 mL, 11.6 mmol) was added to a solution of 1-[(4-bromophenyl)sulfonyl]-4-methylpiperazine in (1.24 g, 3.87 mmol; described: in Keasling,

PPPL002-12-17

H. H. et al. *J. Med. Chem.* **1965**, *8*, 548-550) in anhydrous tetrahydrofuran (25 mL) at -78 °C under an atmosphere of nitrogen, followed by dropwise addition of n-butyllithium (9.8 mL, 15.5 mmol). The resulting mixture was stirred at -78 °C for 30 min, then allowed to warm to room temperature. HCl (3 M aq, 7.8 mL, 23.2 mmol) was added and the mixture was stirred at room temperature for 10 min. Sodium carbonate (4.1 g, 38.7 mmol) was added followed by the addition of methyl 3-amino-6-bromo-2-pyrazinecarboxylate (0.79 g, 3.4 mmol) and Pd(dppf)Cl₂ (95 mg, 0.12 mmol). The resulting mixture was heated at 55 °C overnight. Silica was added, the solvent was evaporated and the crude mixture was purified by column chromatography on silica using chloroform/methanol, (99:1), as the eluent to give 0.923 g (69% yield) of the base as a yellow solid: ¹HNMR (DMSO-d₆) δ 9.0 (s, 1 H), 8.22 (d, J = 7 Hz, 2 H), 7.80 (d, J = 7 Hz, 2 H), 7.62 (br s, 2 H), 3.90 (s, 3 H) 2.91 (m, 4 H), 2.36 (m, 4 H), 2.12 (s, 3 H); ¹³CNMR (DMSO-d₆) δ 166.2, 155.1, 145.8, 140.33, 127.5, 134.0, 128.1, 125.7, 109.1, 53.5, 52.3, 45.7, 45.2; MS (ESP) m/z 392 (M⁺+1).

15 Example 10

3-Amino-6-[4-[(4-methyl-1-piperazinyl)sulfonyl]phenyl]-2-pyrazinecarboxylic acid
Methyl 3-amino-6-[4-[(4-methyl-1-piperazinyl)sulfonyl]phenyl]pyrazine-2-carboxylate was dissolved in anhydrous tetrahydrofuran (10mL). Lithium hydroxide (0.113 g, 4.72 mmol) in water (19 mL) was added at room temperature and the resulting mixture was stirred at 50 °C for 3 h. The tetrahydrofuran was evaporated and the pH of the water phase was adjusted to 6 with HCl (aq). The precipitated product was filtered and washed with water and dried to give 0.763 g (86% yield) of the title compound a pale yellow solid: ¹HNMR (TFA) δ 8.83 (s, 2 H), 8.23 (m, 2 H), 7.97 (m, 2 H), 4.09 (m, 2 H), 3.76 (m, 2 H), 2.25 (m, 2 H), 3.04 (m, 5 H); ¹³CNMR (TFA) δ 165.81, 147.39, 139.5, 139.2, 135.7, 132.1, 131.1, 128.5, 127.3, 53.9, 43.5, 43.2; MS (ESP) m/z 378 (M⁺+1).

Example 11

4-[2-(4-Bromo-2-fluorophenoxy)ethyl]morpholine

A mixture of 4-bromo-2-fluorophenol (0.612 g, 3.2 mmol; described: in Finger et al. *J. Amer. Chem. Soc.* **1959**, *81*, 94), 4-(2-hydroxyethyl)morpholine (0.47 ml, 3.84 mmol) and triphenylphosphine (1.0 g, 3.84 mmol) was dissolved in anhydrous tetrahydrofuran (5 mL)

PRU002-12-17

30

and cooled to 0 °C. Diethyl azodicarboxylate (0.6 mL, 3.84 mmol) was added dropwise and the resulting mixture was stirred at room temperature for 3.5 h. The solvent was evaporated and the residue partitioned between water and methylene chloride. The organic phase was washed twice with a saturated sodium hydrogen carbonate solution, dried

- 5 (MgSO₄) and the solvent was evaporated. The product was purified by column chromatography on silica using a gradient of toluene/acetonitrile, (4:1 to 0:1), as the eluent to give 0.655 g (67% yield) of the title compound as a clear oil: ¹H NMR (CDCl₃) δ 7.21 (d, J = 11 Hz, 1 H), 7.16 (m, 1 H), 6.83 (t, J = 9 Hz, 1 H), 4.14 (t, J = 6 Hz, 2 H), 3.71 (t, J = 5 Hz, 4 H), 2.80 (t, J = 6 Hz, 2 H), (t, J = 5 Hz, 4 H); ¹³C NMR (CDCl₃, 100) δ 154.2, 151.7, 146.5, 146.4, 127.4, 127.4, 120.1, 119.9, 116.8, 116.8, 112.7, 112.7, 68.1, 67.1, 57.6, 54.3; MS (ESP) m/z 304, 306 (M⁺+1).
- 10

Example 12

4-Bromo-N-(1-ethyl-3-piperidinyl)benzenesulfonamide

- 15 3-Amino-1-ethylpiperidine (0.4 mL, 3.13 mmol) was added to a solution of 4-bromo-benzenesulfonyl chloride (0.4 g, 1.56 mmol) in methylene chloride (10 mL) at room temperature. The mixture was stirred overnight. The reaction solution was extracted three times with a aqueous saturated sodium hydrogen carbonate solution, dried (MgSO₄) and evaporated to give 0.533 g (93% yield) of a light brown solid: ¹H NMR (CDCl₃) δ 7.74 (d, J = 9 Hz, 2 H), 7.62 (d, J = 9 Hz, 2 H), 3.45 (br s, 1 H), 2.46 (br s, 1 H), 2.27 (m, 2 H), 2.23 (m, 2 H), 2.13 (m, 1 H), 1.64 (m, 1 H), 1.45 (m, 3 H), 0.93 (t, J = 7 Hz, 3 H); ¹³C NMR (CDCl₃) δ 140.7, 132.5, 128.7, 127.5, 53.2, 52.3, 49.7, 21.9, 12.1; MS (ESP) m/z 347, 349 (M⁺+1).
- 20
- 25

The following Examples, 13-14, were synthesized as described for Example 12:

Example 13

4-Bromo-N,N-bis(2-methoxyethyl)benzenesulfonamide

- 30 Starting materials: bis(2-methoxyethyl)amine and 4-bromobenzenesulfonyl chloride. Yield: 99% as a yellow oil: ¹H NMR (CDCl₃) δ 7.69 (d, J = 9 Hz, 2 H), δ 7.62 (d, J = 9 Hz, 2 H), 3.49 (m, 4 H), 3.39 (m, 4 H), 3.27 (s, 6 H); MS (ESP) m/z 352, 354 (M⁺+1).

Example 14**4-bromo-N-(3-methylbutyl)-benzenesulfonamide**

Starting materials: isoamylamine and 4-bromobenzenesulfonyl chloride. Yield 98% as a

white solid: ^1H NMR (CDCl_3) δ 7.71 (d, $J = 9$ Hz, 2 H), 7.62 (d, $J = 9$ Hz, 2 H), 4.26 (br s, 1 H), 2.82 (t, $J = 7$ Hz, 2 H), 1.52 (m, 1 H), 1.30 (q, $J = 7$ Hz, 2 H), 0.86 (s, 3 H), 0.84 (s, 3 H); ^{13}C NMR (CDCl_3) δ 139.3, 132.6, 128.8, 127.7, 41.7, 38.6, 25.6, 22.8, 22.4; MS (ESI) m/z 306, 308 (M^++1).

Example 15**Methyl 3-{{[2,6-dimethoxy-4-(2-phenylethoxy)benzyl]amino}-6-[4-(pyrrolidin-1-ylsulfonyl)phenyl]pyrazine-2-carboxylate polystyrene**

Sodium triacetoxyborohydride (2.6 g, 12.2 mmol) in *N,N*-dimethylformamide/acetic acid (98:2, 20 mL) and trimethylsilyl chloride (1.17 mL, 9.18 mmol) were added to a mixture of methyl 3-amino-6-[4-(pyrrolidin-1-ylsulfonyl)phenyl]pyrazine-2-carboxylate (4.4 g, 12.2 mmol) and 2-(3,5-dimethoxy-4-formylphenoxy) ethyl polystyrene (12 g, 0.51 mmol/g) in *N,N*-dimethylformamide (60 mL). The mixture was shaken for 3 h and then filtered. The polystyrene resin was washed, three times, with *N,N*-dimethylformamide and three times with dichlorormethane. The procedure was repeated using sodium triacetoxyborohydride (2.6 g, 12.24 mmol) in *N,N*-dimethylformamide/acetic acid, (98:2, 20 mL), trimethylsilyl chloride (1.17 ml, 9.18 mmol) and methyl 3-amino-6-[4-(pyrrolidin-1-ylsulfonyl)phenyl]pyrazine-2-carboxylate (12 g, 0.51 mmol/g) and shaking was continued for 18 h. The polystyrene resin was washed, three times, with *N,N*-dimethylformamide, three times with dichlorormethane and three times with methanol. The resin was dried under vacuum and gave 12.5 g of the title compound.

Analysis: The title compound (50 mg) was treated with trifluoroacetic acid in dichlorormethane (conc. 95%) for 30 min, filtered and the solvent was analyzed by MS: MS (ESI) $363 m/z$ (M^++1) (which corresponds to the starting material).

Example 16**3-{{[2,6-Dimethoxy-4-(2-phenylethoxy)benzyl]amino}-6-[4-(pyrrolidin-1-ylsulfonyl)phenyl]pyrazine-2-carboxylic acid polystyrene**

PPU102-12-17

A solution of lithium hydroxide (4 M, 10 mL) was added to a suspension of methyl 3-
 {[2,6-dimethoxy-4-(2-phenylethoxy)benzyl]amino}-6-[4-(pyrrolidin-1-
 ylsulfonyl)phenyl]pyrazine-2-carboxylate polystyrene (12 g, 0.51 mmol/g) in
 tetrahydrofuran (100 mL). The mixture was shaken for 17 h. Filtering and washing of the
 5 resin three times with *N,N*-dimethylformamide/water, (4:1), and three times with *N,N*-
 dimethylformamide/acetic acid, (98:2,) and three times with methanol and drying of the
 resin gave 11.8 g of the title compound.

Analysis: The title compound (50 mg) was treated with trifluoroacetic acid in
 dichloromethane (conc. 95%) for 30 min, filtered and the solvent was analyzed by MS:
 10 MS (ESI) 349 *m/z* (M^++1).

Example 17

3-Amino-6-[4-({[(1*R*)-2-methoxy-1-methylethyl]amino}sulfonyl)phenyl]-*N*-pyridin-3-ylpyrazine-2-carboxamide hydrochloride.

15 *n*-Butyllithium (1.3 mL, 2.1 mmol) was added dropwise over 30 min to a cooled (-78 °C)
 solution of 4-bromo-*N*-[(1*R*)-2-methoxy-1-methylethyl]benzenesulfonamide (0.125 g,
 0.406 mmol) and triisopropyl borate (0.28 mL, 1.2 mmol) in anhydrous tetrahydrofuran
 (10 mL) under nitrogen atmosphere. The reaction mixture was stirred for 2 h at -78 °C.
 HCl (aq, 3 M, 0.81 mL) was added to the reaction mixture and the mixture was allowed to
 20 warm to room temperature. Sodium carbonate (0.516 g, 4.9 mmol) was added followed by
 Pd(dppf)Cl₂ (16 mg, 20 µmol) and 3-amino-6-bromo-*N*-pyridin-3-ylpyrazine-2-
 carboxamide (0.143 g, 0.487 mmol). Tetrahydrofuran (10 mL) was added and the mixture
 was heated to 65 °C for 15 h. The solvent was removed and purification by column
 chromatography using gradient methylene chloride to methylene chloride/methanol, (2:1),
 25 as the eluent gave a yellow solid. The solid was dissolved in methylene chloride (10 mL)
 and HCl in diethyl ether (1 M 2.5 ml) was added. A yellow precipitate was formed.
 Filtering and drying gave 73 mg (35% yield) of the title compound as yellow solid: ¹H
 NMR (D₂O, 400 MHz) δ 9.28 (s, 1 H), 8.53 (s, 3 H), 8.0 (m, 1 H), 7.96 (d, *J* = 8 Hz, 2 H),
 7.70 (d, *J* = 8 Hz, 2 H), 3.42 (m, 1 H), 3.27 (m, 1 H), 3.16 (s, 3 H), 0.93 (d, *J* = 7 Hz, 3 H);

Example 18**3-Amino-6-[4-({(1S)-2-methoxy-1-methylethyl}amino}sulfonyl)phenyl]-N-pyridin-3-ylpyrazine-2-carboxamide hydrochloride**

The title compound was prepared as described for Example 17 using 4-bromo-N-[(1S)-2-methoxy-1-methylethyl]benzenesulfonamide. Yield: 77 % of the title compound as yellow solid: ^1H NMR (D_2O , 400 MHz) δ 9.27 (s, 1 H), 8.53 (m, 3 H), 8.0 (d, $J = 8$ Hz, 2 H), 7.99 (m, 1 H), 7.70 (d, $J = 8$ Hz, 2 H), 3.42 (m, 1 H), 3.26 (d, m, 2 H), 3.25 (s, 3 H), 0.92 (d, $J = 6$ Hz, 3 H); MS (ESI) $443 m/z$ (M^++1).

Example 19**3-Amino-N-(3-nitrophenyl)-6-[4-(pyrrolidin-1-ylsulfonyl)phenyl]pyrazine-2-carboxamide**

3-Nitroaniline (70 mg, 0.51 mmol), O-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (0.164 g, 0.51 mmol) and 1-hydroxybenzotriazole hydrate (69 mg, 0.51 mmol) were added to 3-[(2,6-dimethoxy-4-(2-phenylethoxy)benzyl]amino)-6-[4-(pyrrolidin-1-ylsulfonyl)phenyl]pyrazine-2-carboxylic acid polystyrene (0.50 g, 0.51 mmol/g, 0.255 mmol) in *N,N*-dimethylformamide (2 mL). The mixture was shaken for 5 min where after *N*-ethyl-*N,N*-diisopropylamine (0.133 mL, 0.765 mmol) was added. The mixture was shaken for 18 h, filtered and washed *N,N*-dimethylformamide and three times with methylene chloride. The product was isolated by treating the resin with trifluoroacetic acid in methylene chloride (conc. 95%) for 30 min and then filtered. The solution was evaporated and purification by preparative HPLC (column: XTerra C8 19x300 mm, eluent: gradient acetonitrile/water, (20:80 to 80:20)), gave 3.1 mg (1.3% yield) of the title compound: ^1H NMR (CDCl_3 , 400 MHz) δ 8.60 (s, 1 H), 7.99 (m, 3 H), 7.80 (m, 3 H), 7.50 (d, $J = 8$ Hz, 2 H), 7.38 (t, $J = 8$ Hz, 1 H), 3.15 (m, 4 H), 1.68 (m, 4 H); MS (ESI) $439 m/z$ (M^++1).

Example 20**3-Amino-6-[4-(pyrrolidin-1-ylsulfonyl)phenyl]-*N*-1*H*-tetrazol-5-ylpyrazine-2-carboxamide.**

The title compound was prepared as described Example 19 using 1*H*-tetrazol-5-amine. Yield: 1.1%; MS (ESI) $416 m/z$ (M^++1).

Example 21

3-Amino-N-(2-methoxyphenyl)-6-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}pyrazine-2-carboxamide hydrochloride

- 5 2-Methoxyaniline (80 mg, 318 mmol) was added to a mixture of 3-amino-6-[4-[(4-methyl-1-piperazinyl)sulfonyl]phenyl]-2-pyrazinecarboxylic acid (80 mg, 212 mmol), O-(benzotriazol-1-yl)-N, N', N'-tetramethyluronium tetrafluoroborate (82 mg, 255 mmol), 1-hydroxybenzotriazole hydrate (34 mg, 255 mmol) and N-ethyl-N,N-diisopropylamine (0.111 mL, 0.637 mmol) in N,N-dimethylformamide (2 mL). The reaction mixture was
10 stirred for 13 h. The reaction was quenched with water (1 mL) and the solvent was evaporated. Purification by preparative HPLC (column: XTerra C8 19x300 mm, eluent: a acetonitrile/water, (20:80 to 80:20, gradient) followed by evaporation of the solvent gave a yellowish solid that was dissolved in methylene chloride (10 mL). HCl in diethyl ether (1 M, 2.5 mL) was added while stirring. Filtration and drying gave 12 mg (12% yield) of the
15 title compound: MS (ESI) 483 m/z (M⁺+1).

The following Examples, 22 – 30, were synthesized as described for Example 21:

Example 22

20 **3-Amino-N-(4-methoxyphenyl)-6-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}pyrazine-2-carboxamide hydrochloride**

Starting material: 4-methoxyaniline. Yield: 62%: MS (ESI) 483 m/z (M⁺+1).

Example 23

25 **3-Amino-N-[2-(aminocarbonyl)phenyl]-6-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}pyrazine-2-carboxamide hydrochloride**

Starting material: 2-aminobenzamide. Yield: 19%: MS (ESI) 496 m/z (M⁺+1).

Example 24

30 **3-Amino-N-[3-(aminocarbonyl)phenyl]-6-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}pyrazine-2-carboxamide hydrochloride**

Starting material: 3-aminobenzamide. Yield: 49%: MS (ESI) 496 m/z (M⁺+1).

Example 25

3-Amino-N-(3-cyanophenyl)-6-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}pyrazine-2-carboxamide hydrochloride

- 5 Starting material: 3-aminobenzonitrile. Yield: 19%: MS (ESI) 478 m/z (M^++1).

Example 26

3-Amino-N-(2-bromophenyl)-6-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}pyrazine-2-carboxamide hydrochloride

- 10 Starting material: 2-bromoaniline. Yield: 20%: MS (ESI) 531, 533 m/z (M^++1).

Example 27

3-Amino-N-(3-bromophenyl)-6-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}pyrazine-2-carboxamide hydrochloride

- 15 Starting material: 3-bromoaniline. Yield: 2.3%: MS (ESI) 531, 533 m/z (M^++1).

Example 28

3-Amino-6-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}-N-1*H*-pyrazol-3-ylpyrazine-2-carboxamide hydrochloride

- 20 Starting material: 1*H*-pyrazol-3-amine. Yield: 36%: MS (ESI) 443 m/z (M^++1).

Example 29

3-Amino-N-[4-(aminocarbonyl)-1*H*-pyrazol-3-yl]-6-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}pyrazine-2-carboxamide hydrochloride

- 25 Starting material: 3-amino-1*H*-pyrazole-4-carboxamide. Yield: 36%: MS (ESI) 486 m/z (M^++1).

Example 30

3-Amino-N-1*H*-imidazol-2-yl-6-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}pyrazine-2-carboxamide hydrochloride

- 30 Starting material: 1*H*-imidazol-2-amine. Yield: 5%: MS (ESI) 443 m/z (M^++1).

Example 31**3-Amino-6-[3-fluoro-4-[2-(4-morpholinyl)ethoxy]phenyl]-N-3-pyridinyl-2-pyrazinecarboxamide hydrochloride**

Triisopropyl borate (0.91 mL, 3.96 mmol) was added to a solution of 4-[2-(4-bromo-2-fluorophenoxy)ethyl]morpholine (0.402 g, 1.32 mmol) in anhydrous tetrahydrofuran (10 mL) at -78 °C under an atmosphere of nitrogen, followed by dropwise addition of n-butyllithium (2.5 mL, 3.96 mmol) over 5 min. The resulting mixture was stirred at -78 °C for 50 min then allowed to warm to room temperature. HCl (3 M aq, 2.2 mL, 6.61 mmol) was added and the mixture was stirred at room temperature for 10 min. Sodium carbonate (1.40 g, 13.2 mmol) was added followed by the addition of 3-amino-6-bromo-N-pyridin-3-ylpyrazine-2-carboxamide (0.272 g, 0.92 mmol) and Pd(dppf)Cl₂ (32 mg, 0.04 mmol). The resulting mixture was heated at 55 °C overnight. Silica was added, the solvent was evaporated and the crude mixture was purified by column chromatography using ethyl acetate as the eluent, followed by chloroform, then using chloroform/methanol, (98:2), to give 0.335 g (58% yield) of the base as a yellow solid: ¹³C NMR (DMSO-d₆) δ 165.4, 154.4, 163.6, 151.2, 146.8, 146.7, 145.3, 144.8, 143.6, 137.8, 134.9, 129.4, 129.4, 129.0, 123.7, 123.4, 122.1, 115.2, 113.9, 113.7, 79.4, 67.0, 6.5, 57.2, 53.9.

Hydrochloric acid in diethyl ether (0.28 mL, 1 M) was added to a solution of the base (0.324 g, 0.74 mmol) in methylene chloride/methanol, (9:1). The yellow precipitate was filtered off, washed with ethyl acetate, and then purified by preparative HPLC (column: Xterra C8 19x300 mm, eluent: a water/acetonitrile/ammonium acetate gradient). The acetonitrile in the fractions that contained the purified product were evaporated, an aqueous saturated sodium hydrogencarbonate solution was added and extracted, twice, with methylene chloride. The organic phase was dried (MgSO₄) and the solvent was evaporated giving the base again. Hydrochloride acid in diethyl ether (0.56 mL, 1 M) was added to a solution of the base (0.123 g, 0.28 mmol) in methylene chloride/methanol, (9:1). The yellow precipitate was filtered off, washed with diethyl ether and dried in vacuo to give 120 mg (90% yield) of the title compound as a yellow solid: ¹H NMR (D₂O) δ 9.37 (d, J = 2 Hz, 1 H), 8.62 (m, 1 H), 8.57 (d, J = 6 Hz, 1 H), 8.55 (s, 1 H), 8.04 (dd, J = 8 and 6 Hz, 1 H), 7.74 (dd, J = 13 and 2 Hz, 1 H), 7.64 (m, 1 H), 7.15 (t, J = 9 Hz, 1 H), 4.49 (t, J = 5 Hz, 2 H), 4.14 (br s, 2 H), 3.91 (br s, 2 H), 3.73 (t, J = 5 Hz, 2 H), 3.66 (br s, 2 H), 3.39 (br s, 2 H); MS (ESP) m/z 440 (M⁺+1).

The following Examples, 32-34, were synthesized as described for Example 31:

Example 32

5 3-Amino-6-[4-[(1-ethyl-3-piperidinyl)amino]sulfonyl]phenyl]-N-3-pyridinyl-2-pyrazinecarboxamide hydrochloride

Starting material: 4-bromo-N-(1-ethyl-3-piperidinyl)benzenesulfonamide. The crude product was purified on silica using chloroform/methanol, (95:5), as the eluent. Yield 39% of the base.

10 Hydrochloride, yield: 71%: ^1H NMR (D_2O) δ 9.38 (s, 1 H), 8.70 (s, 1 H), 8.63 (d, J = 9 Hz, 1 H), 8.59 (d, J = 9 Hz, 1 H), 8.13 (d, J = 8 Hz, 2 H), 8.06 (dd, J = 8 and 6 Hz, 1 H), 7.86 (d, J = 8 Hz, 2 H), 3.55 (m, 1 H), 3.45 (m, 2 H), 3.45 (m, 2 H), 3.12 (m, 2 H), 2.73 (m, 1 H), 1.54 (m, 4 H), 1.31 (t, J = 7 Hz, 1 H), 8.63 (d, J = 7 Hz, 2 H), 1.16 (t, J = 7 Hz, 1 H); ^{13}C NMR (D_2O) δ 165.3, 154.1, 145.5, 140.0, 139.0, 137.6, 137.0, 132.9, 128.0, 127.6, 66.4, 55.3, 52.4, 48.3, 28.4, 21.7, 14.5; MS (TSP) m/z 482 ($M^+ + 1$).

Example 33

3-Amino-6-[4-[[bis(2-methoxyethyl)amino]sulfonyl]phenyl]-N-3-pyridinyl-2-pyrazinecarboxamide hydrochloride

20 Starting material: 4-bromo-*N,N*-bis(2-methoxyethyl)benzenesulfonamide. The crude product was purified on silica using heptane/ethylacetate, (1:1), as eluent. Yield: 62% of the base. ^1H NMR (CDCl_3) δ 9.79 (s, 1 H), 8.82 (s, 1 H), 8.73 (s, 1 H), 8.41 (d, J = 8 Hz, 1 H), 8.25 (m, 1 H), 8.03 (d, J = 8 Hz, 2 H), 7.99 (d, J = 8 Hz, 2 H), 7.33 (m, 1 H), 3.54 (t, J = 6 Hz, 4 H), 3.41 (t, J = 6 Hz, 4 H), 3.25 (s, 6 H); ^{13}C NMR (CDCl_3) δ 164.4, 154.8, 146.0, 145.7, 141.8, 140.1, 139.9, 138.8, 134.2, 128.2, 127.3, 126.2, 124.6, 124.0, 71.7, 59.0, 48.9.

25 Hydrochloride, yield 78%: ^1H NMR ($\text{DMSO}-d_6$) δ 9.38 (s, 1 H), 9.05 (s, 1 H), 8.88 (d, J = 8 Hz, 1 H), 8.65 (d, J = 5 Hz, 1 H), 8.42 (d, J = 8 Hz, 2 H), 8.03 (m, 1 H), 7.87 (d, J = 8 Hz, 2 H), 3.41 (t, J = 6 Hz, 4 H), 3.30 (t, J = 6 Hz, 4 H), 3.18 (s, 6 H); MS (ESP) m/z 487 ($M^+ + 1$).

RECEIVED
JULY 12 2017**Example 34****3-Amino-6-[4-[(3-methylbutyl)amino]sulfonyl]phenyl]-N-3-pyridinyl-2-pyrazinecarboxamide hydrochloride**

Starting material: 4-bromo-N-(3-methylbutyl)benzenesulfonamide. The crude product was purified on silica using heptane/ethylacetate, (2:1 to 1:2), as eluent. Yield: 62% of the base:

¹H NMR (DMSO-d₆) δ 9.03 (s, 1 H), 8.99 (d, J = 2 Hz, 1 H), 8.42 (d, J = 8 Hz, 2 H), 8.33 (m, 1 H), 8.18 (m, 1 H), 7.87 (d, J = 8 Hz, 2 H), 7.83 (br s, 2 H), 7.61 (m, 1 H), 7.39 (dd, J = 8 and 5 Hz, 1 H), 2.69 (q, J = 7 Hz, 2 H), 1.50 (sept, J = 7 Hz, 1 H), 1.20 (q, J = 7 Hz, 2 H), 0.80 (s, 3 H), 0.78 (s, 3 H).

Hydrochloride, yield 78%: ¹H NMR (DMSO-d₆) δ 9.38 (d, J = 2 Hz, 1 H), 9.05 (s, 1 H), 8.91 (d, J = 9 Hz, 1 H), 8.69 (d, J = 5 Hz, 1 H), 8.45 (d, J = 8 Hz, 2 H), 8.06 (dd, J = 9 and 6 Hz, 1 H), 7.84 (d, J = 8 Hz, 2 H), 7.62 (br s, 1 H), 2.71 (br s, 2 H), 1.50 (sept, J = 7 Hz, 1 H), 1.23 (quart, J = 7 Hz, 2 H), 0.80 (s, 3 H), 0.78 (s, 3 H); MS (ESP) m/z 442 (M⁺+1).

Example 35**3-Amino-6-[4-[[[(1*S*)-2-methoxy-1-methylethyl]amino]carbonyl]phenyl]-N-3-pyridinyl-2-pyrazinecarboxamide hydrochloride**

Triethylamine (0.12 mL, 0.89 mmol) was added to a mixture of 4-{5-amino-6-[(pyridin-3-ylamino)carbonyl]pyrazin-2-yl}benzoic acid (100 mg, 0.30 mmol), O-(benzotriazol-1-yl)-

N,N,N',N'-tetramethyluronium tetrafluoroborate (0.105 g, 0.33 mmol) and 1-hydroxybenzotriazole (44 mg, 0.33 mmol) in methylene chloride/methanol (9:1, 10 mL) at room temperature. (*S*)-(+)1-methoxy-2-propylamine was added dropwise and the resulting mixture was stirred at room temperature for 1.5 h. The mixture was evaporated onto silica and purified by chromatography on silica using toluene/acetonitrile, (2:1 to 0:1) as the eluent. The formed yellow solid was dissolved in methylene chloride. Hydrochloride acid in diethyl ether (0.4 mL, 1 M) was added and the mixture was stirred at room temperature.

The precipitated product was filtrated off and dried in vacuo at 40 °C giving 39 mg (29% yield) of the product as a yellow solid. ¹H NMR (DMSO-d₆) δ 9.38 (m, 1 H), 9.08 (s, 1 H), 8.85 (d, J = 9 Hz, 1 H), 8.67 (d, J = 5 Hz, 1 H), 8.36 (d, J = 8 Hz, 2 H), 8.32 (d, J = 8 Hz, 2 H), 8.03 (m, J = 6 Hz, 1 H), 7.99 (d, J = 8 Hz, 2 H), 7.80 (br s, 1 H), 4.23 (m, 1 H), 3.45 (m, 1 H), 3.32 (m, 1 H), 3.29 (s, 3 H), 1.17 (d, J = 7 Hz, 3 H); ¹³C NMR (D₂O) δ 165.8,

30

165.5, 154.9, 146.3, 138.2, 138.1, 137.5, 135.6, 134.3, 128.0, 126.9, 125.6, 123.0, 75.3, 58.4, 44.8, 17.6; MS (ESP) m/z 407 (M^++1).

Example 36

5 **3-Amino-N-3-pyridinyl-6-[4-[[[2-(1-pyrrolidinyl)ethyl]amino]carbonyl]phenyl]-2-pyrazinecarboxamide hydrochloride**

The title compound was prepared as described for Example 35 using 1-(2-aminoethyl)pyrrolidine. The crude product was purified on silica using chloroform/methanol, (95:5), as eluent. Hydrochloride, yield 23%; 1H NMR (D_2O) δ 9.33 (s, 1 H), 8.67 (s, 1 H), 8.55 (d, J = 6 Hz, 2 H), 8.0 (m, 3 H), 7.82 (d, J = 8 Hz, 2 H), 3.83 (t, J = 6 Hz, 4 H), 4.53 (t, J = 6 Hz, 2 H), 3.23 (m, 2 H), 2.23 (m, 2 H), 2.09 (m, 2 H); ^{13}C NMR (D_2O) δ 170.3, 165.4, 154.0, 145.5, 138.8, 137.5, 136.4, 133.6, 132.7, 128.2, 127.6, 125.7, 123.8, 55.0, 54.3, 36.6, 23.0; MS (ESP) m/z 432 (M^++1).

15 **Example 37**

3-Amino-N-(3-methoxyphenyl)-6-[4-[(4-methyl-1-piperazinyl)sulfonyl]phenyl]-2-pyrazinecarboxamide hydrochloride

Triethylamine (0.48 mL, 3.44 mmol) was added to a mixture of 3-amino-6-bromo-2-pyrazinecarboxylic acid (0.25 g, 1.15 mmol; described in: Ellingsson, R. C.; Henry, R. L. J. 20 *Am. Chem. Soc.* 1949, 2798-2800), O-(benzotriazol-1-yl)- N,N,N',N' -tetramethyluronium tetrafluoroborate (0.405 g, 1.26 mmol) and 1-hydroxybenzotriazole (0.17 g, 1.26 mmol) in N,N -dimethylformamide/acetonitrile, (1:1, 5mL). After stirring for 0.5 h at room temperature, 3-methoxyaniline (0.15 mL, 1.38 mmol) was added and the resulting mixture was stirred overnight at room temperature. Water (5-10 mL) was added and the precipitate was filtered off and washed with water to give 0.25 g (68% yield) of a yellow solid: MS (ESP) m/z 323, 325 (M^++1).

The solid (0.19 g, 0.59 mmol) from previous step was dissolved in tetrahydrofuran/water, (5:1, 5mL), together with [4-[(4-methyl-1-piperazinyl)sulfonyl]phenyl]boronic acid (0.25 g, 0.88 mmol), sodium carbonate (0.187 g, 1.76 mmol) and Pd(dppf)Cl₂ (14 mg, 0.018 mmol). The resulting mixture was stirred at 70 °C overnight (N₂-atmosphere). The mixture was evaporated onto silica and purified by chromatography using a gradient toluene/acetonitrile, (4:1 to 1:2), as the eluent to give 82 mg (29% yield) a yellow solid

which was dried in vacuo at 40 °C. 48 mg of the base was dissolved in a methylene chloride/methanol mixture, (9:1), and hydrochloride acid in diethyl ether (0.13 mL, 1 M) was added. The precipitate was washed with diethyl ether and dried in vacuo to give 37 mg (63% yield) of the title compound: ^1H NMR (DMSO- d_6) δ 9.05 (s, 1 H), 8.54 (d, J = 8 Hz, 2 H), 7.86 (d, J = 8 Hz, 2 H), 7.51 (m, 1 H), 7.44 (d, J = 8 Hz, 1 H), 7.30 (m, 1 H), 6.75 (m, 1 H), 3.83 (d, J = 12 Hz, 2 H), 3.78 (s, 3 H), 3.44 (m, 2 H), 3.16 (m, 2 H), 2.73 (m, 5 H); ^{13}C NMR (DMSO- d_6) δ 164.3, 159.5, 154.7, 145.4, 140.6, 139.0, 136.2, 133.4, 129.4, 128.0, 126.4, 124.5, 113.3, 109.8, 106.8, 55.1, 51.5, 43.1, 41.9; MS (ESP) m/z 483 ($M^+ + 1$).

The following Examples, 38 – 41, were synthesized as described for Example 37.

Example 38

***N*-(3-Acetylphenyl)-3-amino-6-[4-[(4-methyl-1-piperazinyl)sulfonyl]phenyl]-2-pyrazinecarboxamide hydrochloride**

Starting material: 3-acetylaniline. The title compound was purified by chromatography on silica gel using a gradient toluene/acetonitrile, (4:1 to 0:1), as the eluent, followed by formation of the hydrochloride salt, yield 2%: ^1H NMR (DMSO- d_6) δ 10.7 (s, 1 H), 9.07 (s, 1 H), 8.57 (d, J = 8 Hz, 2 H), 8.43 (s, 1 H), 8.12 (d, J = 9 Hz, 1 H), 7.87 (d, J = 8 Hz, 2 H), 7.78 (d, J = 8 Hz, 1 H), 7.56 (d, J = 8 Hz, 1 H), 3.84 (d, J = 12 Hz, 2 H), 3.46 (d, J = 12 Hz, 2 H), 3.17 (m, 2 H), 2.75 (s, 3 H), 2.70 (m, 2 H), 2.62 (s, 3 H); ^{13}C NMR (DMSO- d_6) δ 197.6, 164.6, 154.7, 145.5, 140.6, 138.2, 137.2, 136.2, 133.2, 128.9, 128.0, 126.4, 125.7, 124.2, 120.4, 51.5, 43.0, 41.8, 26.8; MS (ESP) m/z 495 ($M^+ + 1$).

Example 39

***3*-Amino-6-[4-[(4-methyl-1-piperazinyl)sulfonyl]phenyl]-2-pyrazinecarboxamide hydrochloride**

Starting material: 3-trifluoromethylaniline. Purification of the title compound by preparative HPLC (column: Xterra C8 19x300 mm, eluent: a water/acetonitrile/ammonium acetate gradient), followed by formation of the hydrochloride salt gave the title compound in 8% yield: ^1H NMR (DMSO- d_6) δ 8.38 (s, 1 H), 7.71 (m, 2 H), 7.54 (m, 3 H), 7.26 (m, 1 H) 7.0 (m, 2 H), 3.52 (m, 4 H), 3.20 (m, 4 H), 2.95 (s, 3 H); MS (ESP) m/z 521.

PPNU012-12-17

Example 40

N-[3-(Acetylamino)phenyl]-3-amino-6-[4-[(4-methyl-1-piperazinyl)sulfonyl]phenyl]-2-pyrazinecarboxamide

Starting material: 3-aminoacetanilide. The title compound was purified by chromatography on silica gel using a gradient toluene/acetonitrile, (4:1 to 0:1), as the eluent. Yield: 55% of the title compound as a yellow solid: ^1H NMR (DMSO- d_6) δ 10.43, (s, 1 H), 10.01 (s, 1 H), 9.02 (s, 1 H), 8.50 (d, J = 8 Hz, 2 H), 8.09 (s, 1 H), 7.86 (br s, 1 H), 7.81 (d, J = 8 Hz, 2 H), 7.42 (m, 2 H), 7.30 (t, J = 8 Hz, 2 H), 2.96 (br s, 4 H); 2.45 (br s, 4 H), 2.21 (br s, 3 H), 2.06 (s, 3 H); ^{13}C NMR (DMSO- d_6) δ 168.3, 165.3, 154.7, 145.3, 140.3, 139.5, 138.0, 136.4, 133.8, 128.7, 127.9, 126.2, 124.5, 116.2, 115.2, 112.1, 53.3, 45.7, 45.5, 25.1; MS (ESP) m/z 510 ($M^+ + 1$).

Example 41

15 *3-Amino-N-[3-(aminosulfonyl)phenyl]-6-[4-[(4-methyl-1-piperazinyl)sulfonyl]phenyl]-2-pyrazinecarboxamide*

Starting material: 3-aminobenzenesulphonamide. Purification of the title compound by preparative HPLC (column: XTerra C8 19x300 mm, eluent: a water/acetonitrile/ammonium acetate gradient) gave 9% yield of the title compound as a yellow solid: ^1H NMR (DMSO- d_6) δ 9.04 (s, 1 H), 8.51 (d, J = 8 Hz, 2 H), 8.43 (s, 1 H), 8.01 (m, 1 H), 7.87 (br s, 2 H), 7.81 (d, J = 8 Hz, 2 H), 7.61 (m, 2 H), 7.40 (s, 2 H), 2.94 (m, 4 H), 2.37 (m, 4 H), 2.14 (s, 3 H); ^{13}C NMR (DMSO- d_6) δ 164.7, 154.7, 145.6, 144.6, 140.2, 138.3, 136.6, 133.9, 129.2, 127.9, 126.3, 124.2, 124.1, 121.2, 118.1, 53.5, 45.7, 45.3; MS (ESP) m/z 532 ($M^+ + 1$).

Example 42

4-{5-Amino-6-[(pyridin-3-ylamino)carbonyl]pyrazin-2-yl}benzoic acid

Pd(PPh₃)₄ (1.05 g, 0.91 mmol) was added to a solution of 3-amino-6-bromo-*N*-pyridin-3-ylpyrazine-2-carboxamide (2.0 g, 6.8 mmol), 4-carboxyphenylboronic acid (1.12 g, 6.7 mmol), and sodium carbonate (2.88 g, 27.2 mmol) in tetrahydrofuran/water, (1:1, 240 mL),

and the resulting mixture was heated at 75°C for 16 days. The solvent was evaporated and the residue dissolved in water. The aqueous phase was washed with ethyl acetate and then

neutralized (pH 7) using HCl (10% aq.). The formed crystals were filtered off and dried in vacuo to give 1.7 g (77% yield) of the title compound: MS (ES) *m/z* 336 (M^++1).

Example 42

- 5 **3-Amino-6-(4-[(2-ethoxyethyl)amino]sulfonyl)phenyl)-*N*-pyridin-3-ylpyrazine-2-carboxamide hydrochloride**

The title compound was prepared as described Example 17 using 4-bromo-*N*-(2-ethoxyethyl)benzenesulfonamide. Yield: 10 %: ^1H NMR (D_2O , 400 MHz) δ 9.29 (d, $J = 3$ Hz, 1 H), 8.56 (s, 1 H), 8.54 (m, 1 H), 8.52 (m, 1 H), 8.01 (dd, $J = 9, 6$ Hz, 1 H), 7.98 (d, $J = 9$ Hz, 2 H), 7.71 (d, $J = 9$ Hz, 2 H), 3.45 (t, $J = 5$ Hz, 2 H), 3.41 (q, $J = 7$ Hz, 2 H), 3.07 (t, $J = 5$ Hz, 2 H), 1.05 (t, $J = 7$ Hz, 3 H); MS (ES) *m/z* 443 (M^++1).

Pharmaceutical compositions

- 15 According to one aspect of the present invention there is provided a pharmaceutical composition comprising a compound of formula I, as a free base or a pharmaceutically acceptable salt, solvate or solvate of salt thereof, for use in the prevention and/or treatment of conditions associated with glycogen synthase kinase-3.
- 20 The composition may be in a form suitable for oral administration, for example as a tablet, for parenteral injection as a sterile solution or suspension. In general the above compositions may be prepared in a conventional manner using pharmaceutical carriers or diluents. Suitable daily doses of the compounds of formula I in the treatment of a mammal, including man, are approximately 0.01 to 250 mg/kg bodyweight at peroral administration and about 0.001 to 250 mg/kg bodyweight at parenteral administration. The typical daily dose of the active ingredients varies within a wide range and will depend on various factors such as the relevant indication, the route of administration, the age, weight and sex of the patient and may be determined by a physician.
- 25 A compound of formula I, or a pharmaceutically acceptable salt, solvate or solvate of salt thereof, can be used on its own but will usually be administered in the form of a

pharmaceutical composition in which the formula I compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable diluent or carrier. Dependent on the mode of administration, the pharmaceutical composition may comprise from 0.05 to 99 %w (per cent by weight), for example from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

A diluent or carrier includes water, aqueous poly(ethylene glycol), magnesium carbonate, magnesium stearate, talc, a sugar (such as lactose), pectin, dextrin, starch, tragacanth, microcrystalline cellulose, methyl cellulose, sodium carboxymethyl cellulose or cocoa butter.

A composition of the invention can be in tablet or injectable form. The tablet may additionally comprise a disintegrant and/or may be coated (for example with an enteric coating or coated with a coating agent such as hydroxypropyl methylcellulose).

15

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula I, or a pharmaceutically acceptable salt, solvate or solvate of salt thereof, a hereinbefore defined, with a pharmaceutically acceptable diluent or carrier.

20

An example of a pharmaceutical composition of the invention is an injectable solution containing a compound of the invention, or a pharmaceutically acceptable salt, solvate or solvate of salt thereof, as hereinbefore defined, and sterile water, and, if necessary, either sodium hydroxide or hydrochloric acid to bring the pH of the final composition to about pH 5, and optionally a surfactant to aid dissolution.

Liquid solution comprising a compound of formula I, or a salt thereof, dissolved in water.

<u>Solution</u>	<u>mg/mL</u>
Compound X	5.0% w/v
Pure water	To 100%

Medical use

Surprisingly, it has been found that the compounds defined in the present invention, as a free base or a pharmaceutically acceptable salt thereof, are well suited for inhibiting

- 5 glycogen synthase kinase-3 (GSK3). Accordingly, the compounds of the present invention are expected to be useful in the prevention and/or treatment of conditions associated with glycogen synthase kinase-3 activity, i.e. the compounds may be used to produce an inhibitory effect of GSK3 in mammals, including man, in need of such prevention and/or treatment.

10

GSK3 is highly expressed in the central and peripheral nervous system and in other tissues. Thus, it is expected that compounds of the invention are well suited for the prevention and/or treatment of conditions associated with glycogen synthase kinase-3 in the central and peripheral nervous system. In particular, the compounds of the invention are expected 15 to be suitable for prevention and/or treatment of conditions associated with especially, dementia, Alzheimer's Disease, Parkinson's Disease, Frontotemporal dementia Parkinson's Type, Parkinson dementia complex of Guam, HIV dementia, diseases with associated neurofibrillar tangle pathologies and dementia pugilistica.

- 20 Other conditions are selected from the group consisting of amyotrophic lateral sclerosis, corticobasal degeneration, Down syndrome, Huntington's Disease, postencephalitic parkinsonism, progressive supranuclear palsy, Pick's Disease, Niemann-Pick's Disease, stroke, head trauma and other chronic neurodegenerative diseases, Bipolar Disease, affective disorders, depression, schizophrenia, cognitive disorders, hair loss and contraceptive medication.

- 25 Further conditions are selected from the group consisting of pre-demented states, Mild Cognitive Impairment, Age-Associated Memory Impairment, Age-Related Cognitive Decline, Cognitive Impairment No Dementia, mild cognitive decline, mild neurocognitive decline, Late-Life Forgetfulness, memory impairment and cognitive impairment, vascular dementia, dementia with Lewy bodies and androgenetic alopecia.

PRU/02-12-17

45

One embodiment of the invention relates to the prevention and/or treatment of dementia and Alzheimer's Disease.

5 The dose required for the therapeutic or preventive treatment of a particular disease will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated.

10 The present invention relates also to the use of a compound of formula I as defined hereinbefore, in the manufacture of a medicament for the prevention and/or treatment of conditions associated with glycogen synthase kinase-3.

In the context of the present specification, the term "therapy" also includes "prevention" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

15

The invention also provides for a method of treatment and/or prevention of conditions associated with glycogen synthase kinase-3 comprising administering to a mammal, including man in need of such treatment and/or prevention a therapeutically effective amount of a compound of formula I, as hereinbefore defined.

20 **Non-medical use**

In addition to their use in therapeutic medicine, the compounds of formula I as a free base or a pharmaceutically acceptable salt thereof, are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of GSK3 related activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutics agents.

25 **Pharmacology**

Determination of ATP competition in Scintillation Proximity GSK3 β Assay.

GSK3 β scintillation proximity assay.

30 The competition experiments were carried out in duplicate with 10 different concentrations of the inhibitors in clear-bottom microtiter plates (Wallac, Finland). A biotinylated peptide

PCT/GB/2012/051777

substrate, Biotin-Ala-Ala-Glu-Glu-Leu-Asp-Ser-Arg-Ala-Gly-Ser(PO₃H₂)-Pro-Gln-Leu (AstraZeneca, Lund), was added at a final concentration of 1 μM in an assay buffer containing 1 mU recombinant human GSK3β (Dundee University, UK), 12 mM morpholinepropanesulfonic acid (MOPS), pH 7.0, 0.3 mM EDTA, 0.01% β-mercaptorethanol, 0.004 % Brij 35 (a natural detergent), 0.5 % glycerol and 0.5 μg BSA/25 μl. The reaction was initiated by the addition of 0.04 μCi [γ-³³P]ATP (Amersham, UK) and unlabelled ATP at a final concentration of 1 μM and assay volume of 25 μl. After incubation for 20 minutes at room temperature, each reaction was terminated by the addition of 25 μl stop solution containing 5 mM EDTA, 50 μM ATP, 0.1 % Triton X-100 and 0.25 mg streptavidin coated Scintillation Proximity Assay (SPA) beads (Amersham, UK). After 6 hours the radioactivity was determined in a liquid scintillation counter (1450 MicroBeta Trilux, Wallac). The inhibition curves were analysed by non-linear regression using GraphPad Prism, USA. The K_m value of ATP for GSK3β, used to calculate the inhibition constants (K_i) of the various compounds, was 20 μM.

15

The following abbreviations have been used:

MOPS Morpholinepropanesulfonic acid

EDTA Ethylenediaminetetraacetic acid

BSA Bovin Serum Albumin

20 ATP Adenosine Triphosphate

SPA Scintillation Proximity Assay

GSK3 Glycogen synthase kinase 3

25

Results

Typical K_i values for the compounds of the present invention are in the range of about 0.001 to about 10,000 nM. Other values for K_i are in the range of about 0.001 to about 1000 nM. Further values for K_i are in the range of about 0.001 nM to about 300 nM.

30

CLAIMS

1. A compound which is:

5 3-Amino-6-[4-({[(1*R*)-2-methoxy-1-methylethyl]amino}sulfonyl)phenyl]-*N*-pyridin-3-ylpyrazine-2-carboxamide hydrochloride;

10 3-Amino-6-[4-({[(1*S*)-2-methoxy-1-methylethyl]amino}sulfonyl)phenyl]-*N*-pyridin-3-ylpyrazine-2-carboxamide hydrochloride;

15 3-Amino-*N*-(3-nitrophenyl)-6-[4-(pyrrolidin-1-ylsulfonyl)phenyl]pyrazine-2-carboxamide;

20 3-Amino-6-[4-(pyrrolidin-1-ylsulfonyl)phenyl]-*N*-1*H*-tetrazol-5-ylpyrazine-2-carboxamide;

25 3-Amino-6-{4-[(2-ethoxyethyl)amino}sulfonyl}phenyl]-*N*-pyridin-3-ylpyrazine-2-carboxamide hydrochloride;

30 3-Amino-*N*-(2-methoxyphenyl)-6-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}pyrazine-2-carboxamide hydrochloride;

35 3-Amino-*N*-(4-methoxyphenyl)-6-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}pyrazine-2-carboxamide hydrochloride;

40 3-Amino-*N*-[2-(aminocarbonyl)phenyl]-6-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}pyrazine-2-carboxamide hydrochloride;

45 3-Amino-*N*-[3-(aminocarbonyl)phenyl]-6-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}pyrazine-2-carboxamide hydrochloride;

50 3-Amino-*N*-(3-cyanophenyl)-6-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}pyrazine-2-carboxamide hydrochloride;

55 3-Amino-*N*-(2-bromophenyl)-6-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}pyrazine-2-carboxamide hydrochloride;

60 3-Amino-*N*-(3-bromophenyl)-6-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}pyrazine-2-carboxamide hydrochloride;

65 3-Amino-6-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}-*N*-1*H*-pyrazol-3-ylpyrazine-2-carboxamide hydrochloride;

70 3-Amino-*N*-[4-(aminocarbonyl)-1*H*-pyrazol-3-yl]-6-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}pyrazine-2-carboxamide hydrochloride;

75 3-Amino-*N*-1*H*-imidazol-2-yl-6-{4-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}pyrazine-2-carboxamide hydrochloride;

3-amino-6-[3-fluoro-4-[2-(4-morpholinyl)ethoxy]phenyl]-N-3-pyridinyl-2-pyrazinecarboxamide hydrochloride;

5 3-Amino-6-[4-[[1-ethyl-3-piperidinyl)amino]sulfonyl]phenyl]-N-3-pyridinyl-2-pyrazinecarboxamide hydrochloride;

10 3-Amino-6-[4-[[bis(2-methoxyethyl)amino]sulfonyl]phenyl]-N-3-pyridinyl-2-pyrazinecarboxamide hydrochloride;

15 3-Amino-6-[4-[(3-methylbutyl)amino]sulfonyl]phenyl]-N-3-pyridinyl-2-pyrazinecarboxamide hydrochloride;

20 3-Amino-6-[4-[[[(1S)-2-methoxy-1-methylethyl]amino]carbonyl]phenyl]-N-3-pyridinyl-2-pyrazinecarboxamide hydrochloride;

25 3-Amino-N-3-pyridinyl-6-[4-[[[2-(1-pyrrolidinyl)ethyl]amino]carbonyl]phenyl]-2-pyrazinecarboxamide hydrochloride;

30 3-Amino-N-(3-methoxyphenyl)-6-[4-[(4-methyl-1-piperazinyl)sulfonyl]phenyl]-2-pyrazinecarboxamide hydrochloride;

35 N-(3-Acetylphenyl)-3-amino-6-[4-[(4-methyl-1-piperazinyl)sulfonyl]phenyl]-2-pyrazinecarboxamide hydrochloride;

40 3-Amino-6-[4-[(4-methyl-1-piperazinyl)sulfonyl]phenyl]-N-[3-(trifluoromethyl)phenyl]-2-pyrazinecarboxamide hydrochloride;

45 N-[3-(Acetylamino)phenyl]-3-amino-6-[4-[(4-methyl-1-piperazinyl)sulfonyl]phenyl]-2-pyrazinecarboxamide;

50 3-Amino-N-[3-(aminosulfonyl)phenyl]-6-[4-[(4-methyl-1-piperazinyl)sulfonyl]phenyl]-2-pyrazinecarboxamide;

55 as a free base or an alternative pharmaceutically acceptable salt, solvate or solvate of a salt thereof.

2. A compound which is:

3-Amino-6-bromo-N-pyridin-3-ylpyrazine-2-carboxamide;

40 1-[(4-Bromophenyl)sulfonyl]pyrrolidine;

45 4-(Pyrrolidin-1-ylsulfonyl)phenylboronic acid;

50 4-Bromo-N-[(1R)-2-hydroxy-1-methylethyl]benzenesulfonamide;

- 4-Bromo-*N*-[(1*R*)-2-methoxy-1-methylethyl]benzenesulfonamide;
- 4-Bromo-*N*-[(1*S*)-2-methoxy-1-methylethyl]benzenesulfonamide;
- 5 Methyl 3-amino-6-[4-(pyrrolidin-1-ylsulfonyl)phenyl]pyrazine-2-carboxylate;
10. Methyl 3-amino-6-[4-[(4-methyl-1-piperazinyl)sulfonyl]phenyl]pyrazine-2-carboxylate;
- 3-Amino-6-[4-[(4-methyl-1-piperazinyl)sulfonyl]phenyl]-2-pyrazinecarboxylic acid;
- 15 4-[2-(4-Bromo-2-fluorophenoxy)ethyl]morpholine;
- 4-Bromo-*N*-(1-ethyl-3-piperidinyl)benzenesulfonamide;
- 4-Bromo-*N,N*-bis(2-methoxyethyl)benzenesulfonamide;
- 20 4-bromo-*N*-(3-methylbutyl)-benzenesulfonamide;
- Methyl 3-{{[2,6-dimethoxy-4-(2-phenylethoxy)benzyl]amino}-6-[4-(pyrrolidin-1-ylsulfonyl)phenyl]pyrazine-2-carboxylate polystyrene;
- 25 3-{{[2,6-Dimethoxy-4-(2-phenylethoxy)benzyl]amino}-6-[4-(pyrrolidin-1-ylsulfonyl)phenyl]pyrazine-2-carboxylic acid polystyrene;
- 4-(5-Amino-6-[(pyridin-3-ylamino)carbonyl]pyrazin-2-yl}benzoic acid;
- 30 as a free base or a salt, solvate or solvate of a salt thereof,

- 35 3. A pharmaceutical formulation comprising as active ingredient a therapeutically effective amount of the compound according to claim 1 in association with pharmaceutically acceptable carriers or diluents.
- 40 4. The pharmaceutical formulation according to claim 3 for use in the prevention and/or treatment of conditions associated with glycogen synthase kinase-3.
- 40 5. A compound as defined in claim 1 for use in therapy.

6. Use of a compound according to claim 1 in the manufacture of a medicament for prevention and/or treatment of conditions associated with glycogen synthase kinase-3.
7. Use of a compound according to claim 1 in the manufacture of a medicament for prevention and/or treatment of dementia, Alzheimer's Disease, Parkinson's Disease, Frontotemporal dementia Parkinson's Type, Parkinson dementia complex of Guam, HIV dementia, diseases with associated neurofibrillar tangle pathologies and dementia pugilistica.
8. The use according to claim 7 wherein the prevention and/or treatment is Alzheimer's Disease.
9. Use of a compound according to claim 1 in the manufacture of a medicament for prevention and/or treatment of amyotrophic lateral sclerosis, corticobasal degeneration, Down syndrome, Huntington's Disease, postencephalitic parkinsonism, progressive supranuclear palsy, Pick's Disease, Niemann-Pick's Disease, stroke, head trauma and other chronic neurodegenerative diseases, Bipolar Disease, affective disorders, depression, schizophrenia, cognitive disorders, hair loss and contraceptive medication.
10. Use of a compound according to claim 1 in the manufacture of a medicament for prevention and/or treatment of predemented states, Mild Cognitive Impairment, Age-Associated Memory Impairment, Age-Related Cognitive Decline, Cognitive Impairment No Dementia, mild cognitive decline, mild neurocognitive decline, Late-Life Forgetfulness, memory impairment and cognitive impairment, vascular dementia, dementia with Lewy bodies, Frontotemporal dementia and androgenetic alopecia.
11. A method of prevention and/or treatment of conditions associated with glycogen synthase kinase-3, comprising administering to a mammal, including man in need of such prevention and/or treatment, a therapeutically effective amount of a compound of formula I as defined in claim 1.

PRU/M2-12-17

51

12. A method of prevention and/or treatment of dementia, Alzheimer's Disease, Parkinson's Disease, Frontotemporal dementia Parkinson's Type, Parkinson dementia complex of Guam, HIV dementia, diseases with associated neurofibrillar tangle pathologies and dementia pugilistica, comprising administering to a mammal, including man in need of such prevention and/or treatment, a therapeutically effective amount of a compound of formula I as defined in claim 1.
13. The method according to claim 12, wherein the prevention and/or treatment is Alzheimer's Disease.
14. A method of prevention and/or treatment of amyotrophic lateral sclerosis, corticobasal degeneration, Down syndrome, Huntington's Disease, postencephalitic parkinsonism, progressive supranuclear palsy, Pick's Disease, Niemann-Pick's Disease, stroke, head trauma and other chronic neurodegenerative diseases, Bipolar Disease, affective disorders, depression, schizophrenia, cognitive disorders, hair loss and contraceptive medication, comprising administering to a mammal, including man in need of such prevention and/or treatment, a therapeutically effective amount of a compound of formula I as defined in claim 1.
15. A method of prevention and/or treatment of predemented states, Mild Cognitive Impairment, Age-Associated Memory Impairment, Age-Related Cognitive Decline, Cognitive Impairment No Dementia, mild cognitive decline, mild neurocognitive decline, Late-Life Forgetfulness, memory impairment and cognitive impairment, vascular dementia, dementia with Lewy bodies, Frontotemporal dementia and androgenetic alopecia, comprising administering to a mammal, including man in need of such prevention and/or treatment, a therapeutically effective amount of a compound of formula I as defined in claim 1.
16. The use of the intermediates according to claim 2 for the preparation of a compound of formula I as defined in claim 1.

PPR0012-12-17

ABSTRACT

The present invention relates to new compounds, a process for their preparation and new
intermediates used therein, pharmaceutical formulations containing said therapeutically
active compounds and to the use of said active compounds in therapy.

